BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 38/17, 39/395, A61P 37/04 // (A61K 38/17, 31:56) (A61K 39/395, 31:56)

A2

(11) International Publication Number: **WO 00/35472**

(43) International Publication Date: 22 June 2000 (22.06.00)

(21) International Application Number: PCT/IB99/02001

(22) International Filing Date: 15 December 1999 (15.12.99)

(30) Priority Data:
60/112,206 15 December 1998 (15.12.98) US

(71) Applicant *(for all designated States except US)*: HOLLIS–EDEN PHARMACEUTICALS [US/US]; Suite 200, 9333 Genesee Avenue, San Diego, CA 92121 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: PRENDERGAST, Patrick, T. [IE/IE]; Baybush, Straffan, County Kildare (IE).

(74) Agent: ISRAELSEN, Ned, A.; Knobbe, Martens, Olson & Bear, LLP, 16th floor, 620 Newport Center Drive, Newport Beach, CA 92660 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: CYTOKINE COMBINATION THERAPY

(57) Abstract

This invention relates to methods of treatment of persons and animals with indications of immuno–deficiency, wherein the said indication is resultant from viral and/or retroviral, bacterial, fungal or parasitic infection and/or plus infectious protein units. Herein is described the method of administration of an agonist or antagonist to Th_2 cytokines in combination with anti–viral agents or immune enhancing agents. In one aspect of the invention, the agonist or antagonist is a receptor to Interleukin–4 (or mutein receptor) which is administered in combination with an anti–viral agent. Preferred anti–viral/immune–enhancing agents include (a) "compounds of Formula I" (defined herein), and metabolites, analogs and precursors thereof, and pharmaceutically acceptable salts of any such compounds, metabolites, analogs and precursors, (b) protease inhibitors, and (c) reverse transcriptase inhibitors. Additionally herein is described a method of enhancing viral replication as a means of exposing latent infection by the administration of an agonist or antagonist to a Th_2 cytokine. There are also provided such methods comprising administering to a patient at least one Th_2 cytokine and at least one agonist and/or at least one antagonist to said Th_2 cytokine. There are also provided compositions and kits for use in such methods, as well as the use of such compounds in the manufacture of medicaments for treatment for various conditions.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

CYTOKINE COMBINATION THERAPY

Field of the Invention

This invention relates to methods of treatment of patients for enhancing immune response, treating viral infection (including retroviral infection), bacterial infection, fungal infection, parasitic infection and/or infectious protein units in a patient in need of such treatment, or minimizing the likelihood of such infection and/or reducing the potential future adversity of such infection in a patient. The invention further relates to methods of providing immunosuppressive or immunoregulatory effects in a patient. The invention further relates to the use of compounds in the manufacture of medicaments for use in treating a variety conditions, as well as compositions and kits containing the active materials according to the present invention.

Background of the Invention

The Human Immunodeficiency Virus Type I (HIV- I) is the etiological agent of Acquired Immune Deficiency Syndrome (AIDS). AIDS is characterized as a profound breakdown in host's cellular and humoral immunity and increased susceptibility to a wide range of opportunistic infections. One of the consequences of this immune dysfunction is a marked depletion in absolute CD4+ cells in HIV-infected individuals.

The HIV protease enzyme is responsible for post translational processing of *gag* and *gag-pol* polyprotein precursors into their functional products. This aspartyl type protease has been identified as a potential target for antiretroviral therapy, as inhibition of the enzyme results in the production of immature non-infectious virions and subsequent interruption of viral spread.

Summary of the Invention

In accordance with one aspect of the present invention, there are provided methods of treatment of a patient for enhancing immune response, comprising administering to the patient (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th_2 cytokine.

In accordance with another aspect of the present invention, there are provided methods of treating viral infection (including retroviral infection), bacterial infection, fungal infection, parasitic infection and/or infectious protein units in a patient, or minimizing the likelihood of such infection and/or reducing the potential future adversity of such infection in a patient, comprising administering to the patient (1) at least one

anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th_2 cytokine..

Another aspect of the present invention relates to methods of providing immunosuppression or immunoregulatory effect a in patient, comprising administering to the patient (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th_2 cytokine.

The present invention provides methods of treatment of persons and animals with indications of immuno-deficiency, wherein the said indication is resultant from viral and/or retroviral, bacterial, fungal or parasitic infection and/or plus infectious protein units. Herein is described the method of administration of an agonist or antagonist to Th_2 cytokines in combination with anti-viral agents or immune enhancing agents. In one aspect of the invention, the agonist or antagonist is a receptor to Interleukin-4 (or mutein receptor) which is administered in combination with an anti-viral agent. Preferred anti-viral/immune-enhancing agents include (a) "compounds of Formula I" (defined below), and metabolites, analogs and precursors thereof, and pharmaceutically acceptable salts of any such compounds, metabolites, analogs and precursors, (b) protease inhibitors, and (c) reverse transcriptase inhibitors. Additionally herein is described a method of enhancing viral replication as a means of exposing latent infection by the administration of an agonist or antagonist to a Th_2 cytokine.

Also described herein is a method of administration of an agonist or antagonist to Interleukin-4, e.g., preferably a receptor to IL-4 (Interleukin-4), is administered in combination with one or more anti-viral agents for viral treatment. Additionally herein is described a novel treatment regimen which enhances viral replication, thus allowing more effective protease enzyme inhibition wherein the viral enhancing pharmaceutical agent is part of a combination therapy with protease inhibitors and/or reverse transcriptase inhibitors.

The present invention further relates to methods of reducing proviral DHA in patients, and/or facilitating transport into immune cells.

The present invention stems from the novel discovery that peptide/glycopeptide sequences exhibited as components of immature non-infectious virions coat proteins or glycoproteins act in a deleterious manner to human and animal biological functions by binding specifically to the receptor molecules of certain Th_2 cytokines. The presence

of these peptides, polypeptides/glycopeptide sequences which facilitate binding to receptor molecules to Th_2 cytokines is the essential factor, which allows these classes of virions both infectious and non-infectious to inhibit improved immune response. This discovery opens new avenues to treatment and/or prevention by inoculation or therapy of immunosuppressive disorders and/or viral, certain bacterial and/or mycoplasma infections.

Another aspect of this invention relates to combination therapies, one component of which is an agonist or an antagonist to a Th_2, e.g., agonist or antagonist to IL-4, for therapy against indications/disease caused by viral agents. hIL-4 is produced by T-cells and acts as a growth factor for pre-activated B-cells and T-cells. It acts on enriched B-cell populations to produce IgE and on purified B-cells to secrete IgG and IgM. It enhances the generation of cytotoxic T-cells but inhibits the IL-2 (Interleukin-2) dependent generation of lymphocyte-activated killer cells. hIL-4 shows numerous growth and differentiation promoting effects on other hemopoietic lineages. IL-4 elicits its biological activities by binding to specific receptors on the cell surface of IL-4 responsive cells. Binding of IL-4 to its receptor causes rapid receptor internalisation followed by up-regulation of IL-4 receptor expression in the case of a human B lymphoma, human tonsillar B-cells, and mouse T- and B-cells.

This invention further relates to methods of treatment of persons and animals with indications of immuno-deficiency, wherein the said indication is resultant from viral and/or retroviral infection and/or infectious protein units originating from bacterial, fungal or parasitic sources.

In accordance with one aspect of the present invention, there is provided a combination therapy in which (1) one or more anti-viral agent, and (2) recombinant receptor to IL-4, are administered (individually or in any combinations) to a patient to bring about a reduction in the level of proviral DNA (i.e., latent viral cells in the patient's circulation). In a further preferred aspect of the present invention, there is provided a combination therapy in which (1) one or more anti-viral agent, (2) recombinant receptor to IL-4, and (3) IL-4 are administered (individually or in any combinations) to a patient to bring about a reduction in the level of proviral DNA. Where IL-4 is administered in addition to recombinant receptor to IL-4, there is often obtained a further sustainment of reduction in proviral DNA, because this treatment avoids depletion of the patient's

IL-4 resulting from the administration of recombinant receptor to IL-4. Furthermore, binding of recombinant receptor to IL-4 with IL-4 makes it acceptable into immune cells by facilitating transport into the immune cells.

Our studies have established the functional binding and immunosuppressive similarities between certain HIV envelope glycoproteins and specific human Th_2 cytokines.

The acquired immunodeficiency syndrome (AIDS) is characterised by a profound immune dysfunction and opportunistic infections. The immunologic abnormalities include not only the T-helper/inducer lymphocyte subset but also most if not all the major cellular components of the immune system including B lymphocytes, monocytes/macrophages, natural killer cells (NK), and others. Therefore, it is reasonable to expect that in addition to a selective depression of CD4 helper lymphocytes, there exists additional immunoregulatory mechanisms involved in the observed immunodepression of HIV.

Abnormalities in NK (Natural Killer) cell activity have been reported in AIDS patients in spite of an apparently normal number of circulating NK cells. The activity of cell-mediated defence systems is stimulated by consecutive formulation of Interleukin 1β (IL-Iβ), Interleukin-2 (IL-2) and Interferon γ (IFN γ). The system is inhibited by Interleukin-4 (IL-4) and also by prostaglandin E_2 (PGE_2) and histamine, which are released when the immune system is activated.

Interleukin-4 also presents in the transmembrane amino acid sequences of certain viruses including HIV which allow the full vigilance of the immune system to be deflected to a Th_2 system allowing infection to gain a hold and avoid complete viral clearance.

HIV envelope glycoprotein is synthesised as a polyprotein precursor of 160 kDa (gp 160) and is subsequently cleaved into an amino terminus subunit, gp 120, and a carboxy terminus transmembrane subunit, gp41. Lymphocytes from AIDS patients have been reported to secrete a protein with immunosuppressive properties. Mitogen- and antigen-driven blastogenic responses have been shown to be inhibited by purified HIV preparations.

The immunosuppressive properties, including the inhibition of normal human NK cell activity, of the FeL V transmembrane glycoprotein P15E and the suppression of

mitogen- and alloantigen-induced lymphocyte blastogenesis by HIV synthetic peptides 735-752 and 846-860 corresponding to sequences within the HIV transmembrane gp41. Both th se transmembrane HIV peptides were found to have a significant inhibitory effect on NK cell activity, even at doses as low as 0.1 µg/ml.

One of the mechanisms by which the immune system normally regulates itself includes the production of proteins called cytokines. For example, lymphokines are cytokines produced by T-cells and some B-cells, and monokines are cytokines produced by monocytes. Cytokines, which may be glycosylated, mediate numerous immune responses.

IL-4 is a cytokine capable of stimulating production of antibody producing B-cells and which also promotes growth of killer T-cells or cytotoxic T-cells. Additionally, it can inhibit the activity of T-helper cells type 1 (Th1). This in turn may inhibit production of more B-cells or antibody production by more B-cells. Thus, IL-4 is part of an internal regulatory mechanism. A selection of amino acid sequences prepared according to our sequences have demonstrated in a dose dependent manner the ability to down-regulate the expression of Ia molecules on human macrophages similar to Interleukin-4. Some in-vitro experiments suggest that direct T-cell antigen interactions without the mediation of Ia bearing macrophages may result in the generation of antigen specific suppressor T-cells. All experimental evidence indicates that the development of antigen-reactive clones of helper T-cells requires the presence of Ia bearing cells in the tissue. This inhibition of expression on the membrane surface of these class II molecules (Ia) as produced with immunosuppressive cytokines signals the immune system to accept the appearance of new antigens as self to the immune system. Incorporated herein are the following:

-Anti-Viral Agents as per *Rideout et al* U.S. Patent 5,086,044;

-IL-4 Muteins as per *Lee et al* U.S. Patent 5,017,691;

-Interleukin-4 binding protein- as per *Fanslow et al.* U.S. Patent 5,223,605;

-Humanized Monoclonal Antibodies Against Human Interleukin-4 as per *Dalie et al* U.S. Patent 5,597,710;

-Antibodies both polyclonal and monoclonal in human IL-I3 [Interleukin-13] , and purified IL-13 proteins and fragments thereof as per *Culpepper et al* U.S. Patent 5,596,072;

-Anti-Viral agents as per Prendergast U.S. Patent 4,956,355;

-Compounds of the invention include muteins human and murine IL-4s, and nucleic acids which are ffectively homologous to disclosed cDNAs, and/or which are capable of coding for mammalian p IL-4s muteins as per *Lee et al* U.S. Patent 5,656,266;

-Monoclonal antibodies specific to IL-4, IL-5 [Interleukin-5] , IL-6 [Interleukin-6] , and IL-10 [Interleukin-10] as per *Mosmann et al* The Journal of Immunology Vol. 145. 2036-2945. No.9 November 1, 1990;

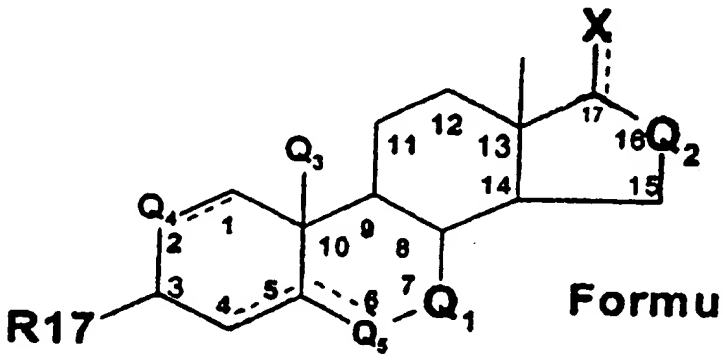
-IL-4 Receptor Proteins as per *Mosley et al* U.S. Patent 5,599,905;

-Cytokines receptor as per *Puri et al* U.S. Patent 5,614,191; and

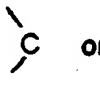
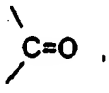
-Anti-Viral Agents as per *Prendergast* U.S. Patent 5,681,831.

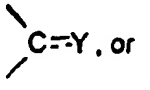
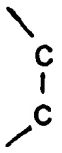
According to the present invention, there is provided agonist or antagonist to Interleukin-4, as part of a combination therapy for use in the prophylaxis and therapy of a viral infection, or a complication or consequence thereof. The viral agent may be any virus, a specific preferred example being the Human Immunodeficiency Virus.

Preferred anti-viral agents include compounds of Formula I:



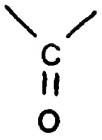
Formula 1

wherein Q_1 is  or  ,

wherein Q_2 is  ,  , or 

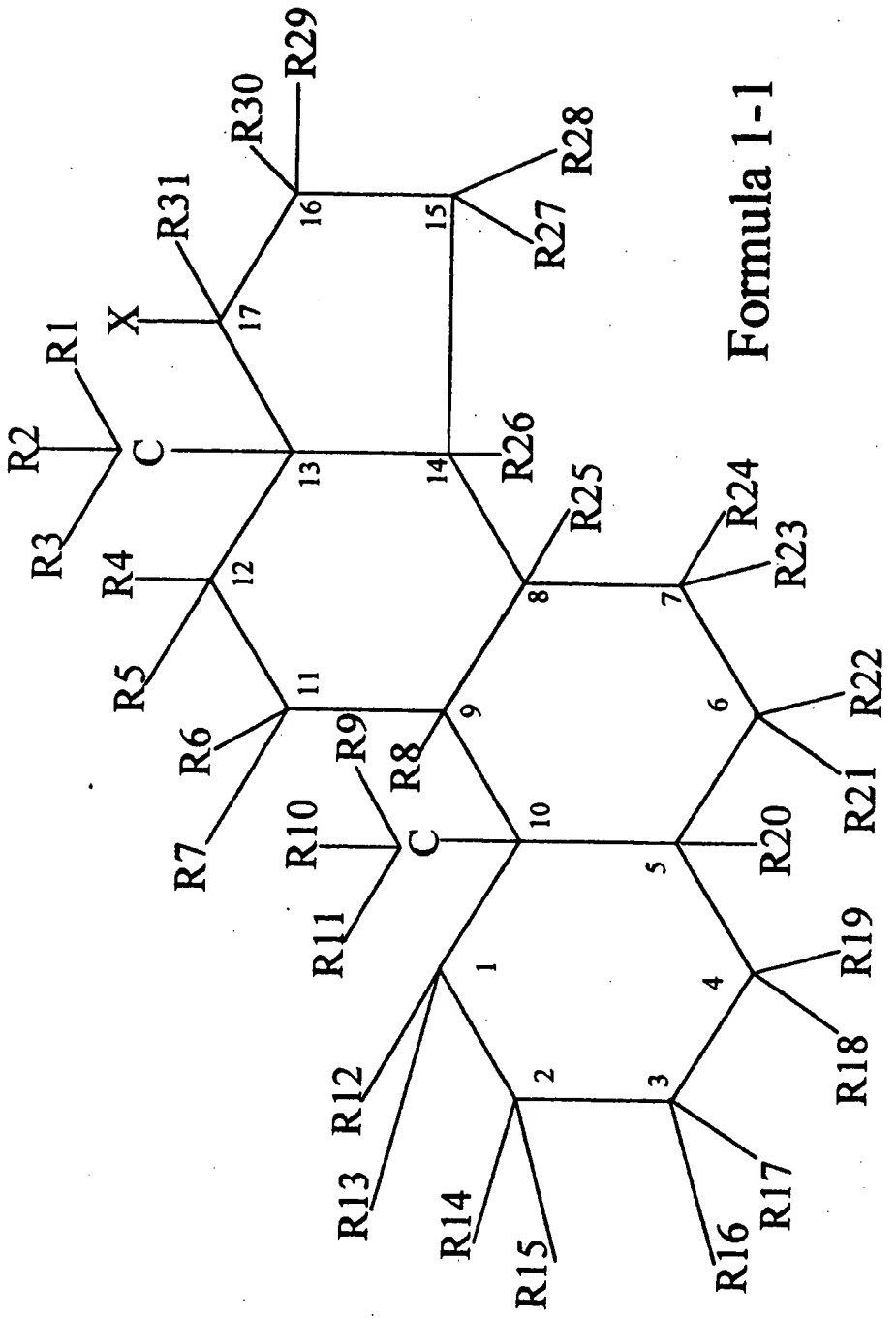
wherein Q_3 is H r CH_3

wherein Q_4 is  hydroxyvinylidene, oxy or methyl methylene;

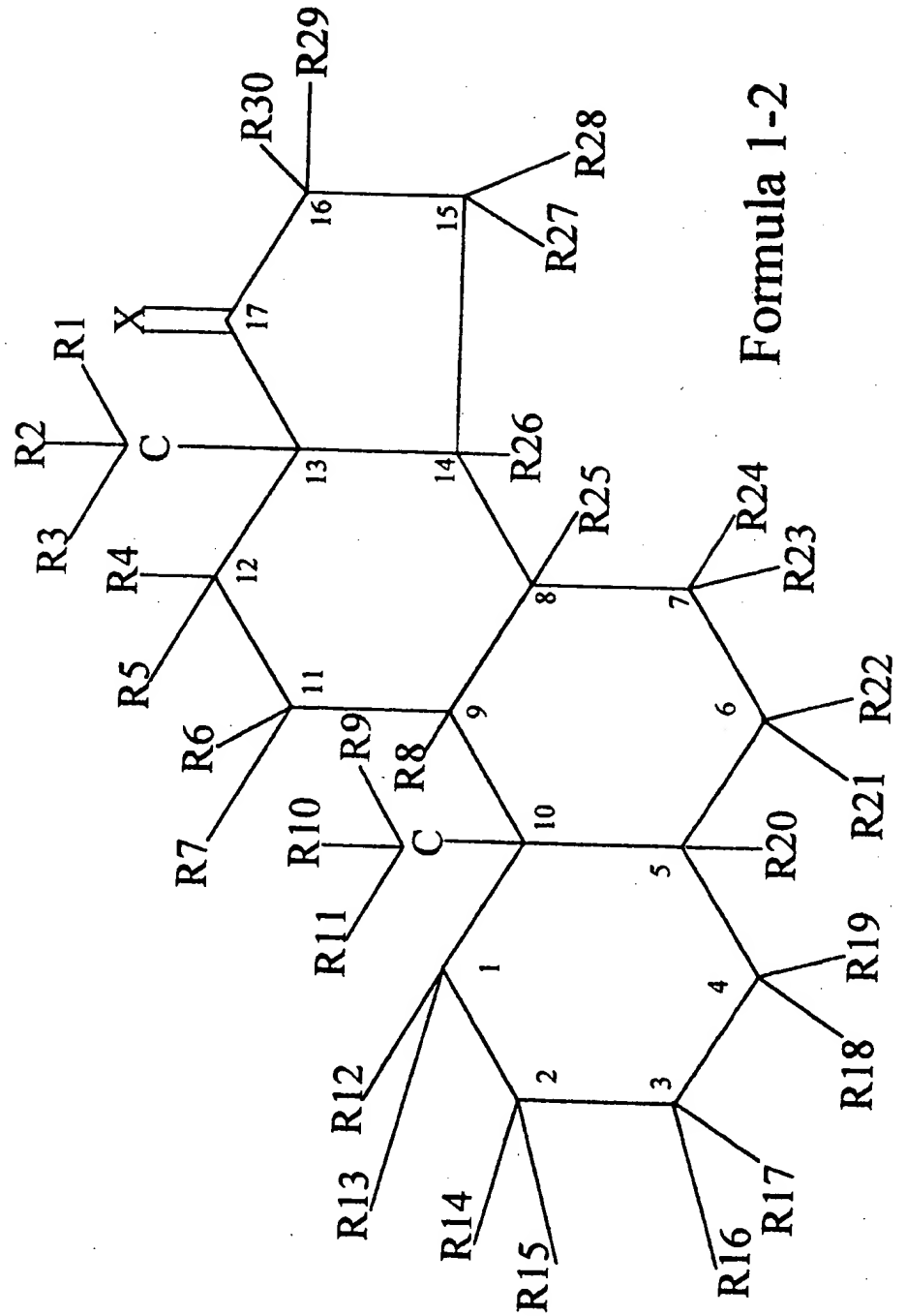
wherein Q_5 is  or 

wherein no hydrogen atoms, some hydrogen atoms or all hydrogen atoms are independently replaced by halogen (such as Br, Cl, F or I), hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkyl or -S-CN,

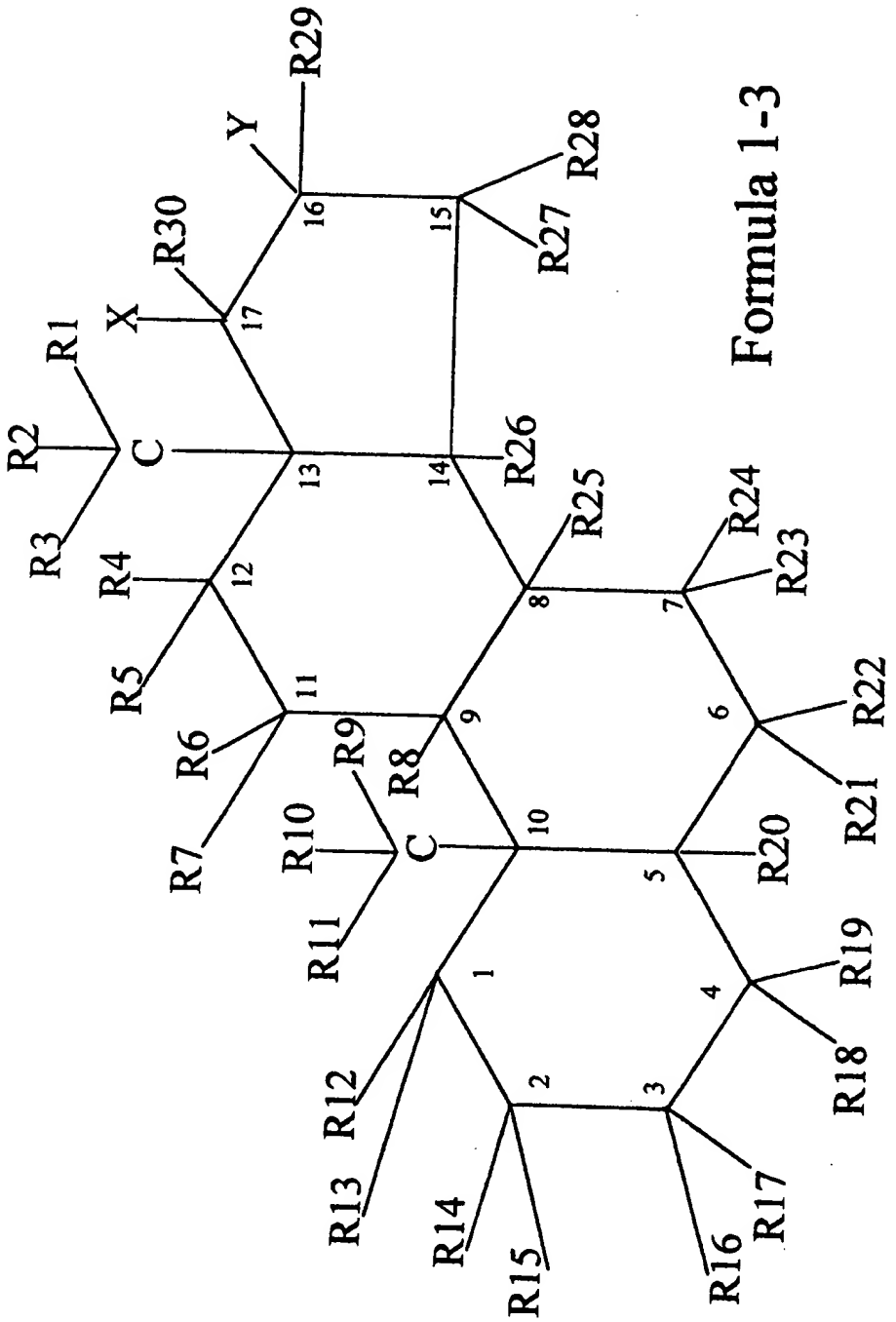
wherein the broken lines between the 1- and 2-positions, the 4- and 5-positions and the 5- and 6- positions, as well as the broken line adjacent the 17 position (attached to X) and the broken line in the definition of Q_2, each independently (where possible, i.e., there cannot be double bonds between both the 4- and 5-position and the 5- and 6-position) represents a single bond or a double bond (where possible, where these bonds are single bonds, the alpha and/or beta configuration is present), i.e., such that in instances where: (1) Q_3 is CH_3, (2) there is a double bond between the 5- and 6-positions and no double bond between the 1- and 2-positions and the 5- and 6-positions, (3) Q_4 is C, and (4) Q_5 is C, Formula 1 encompasses Formulas 1 - 1 through 1 - 24 shown below:


R29
R30
R28
R31
R27
X
R1
R2
C
R3
R26
R4
R25
R24
R5
R23
R6
R22
R9
R8
R7
R10
C
R21
R20
R11
R19
R12
R18
R13
R14
R17
R15
R16
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

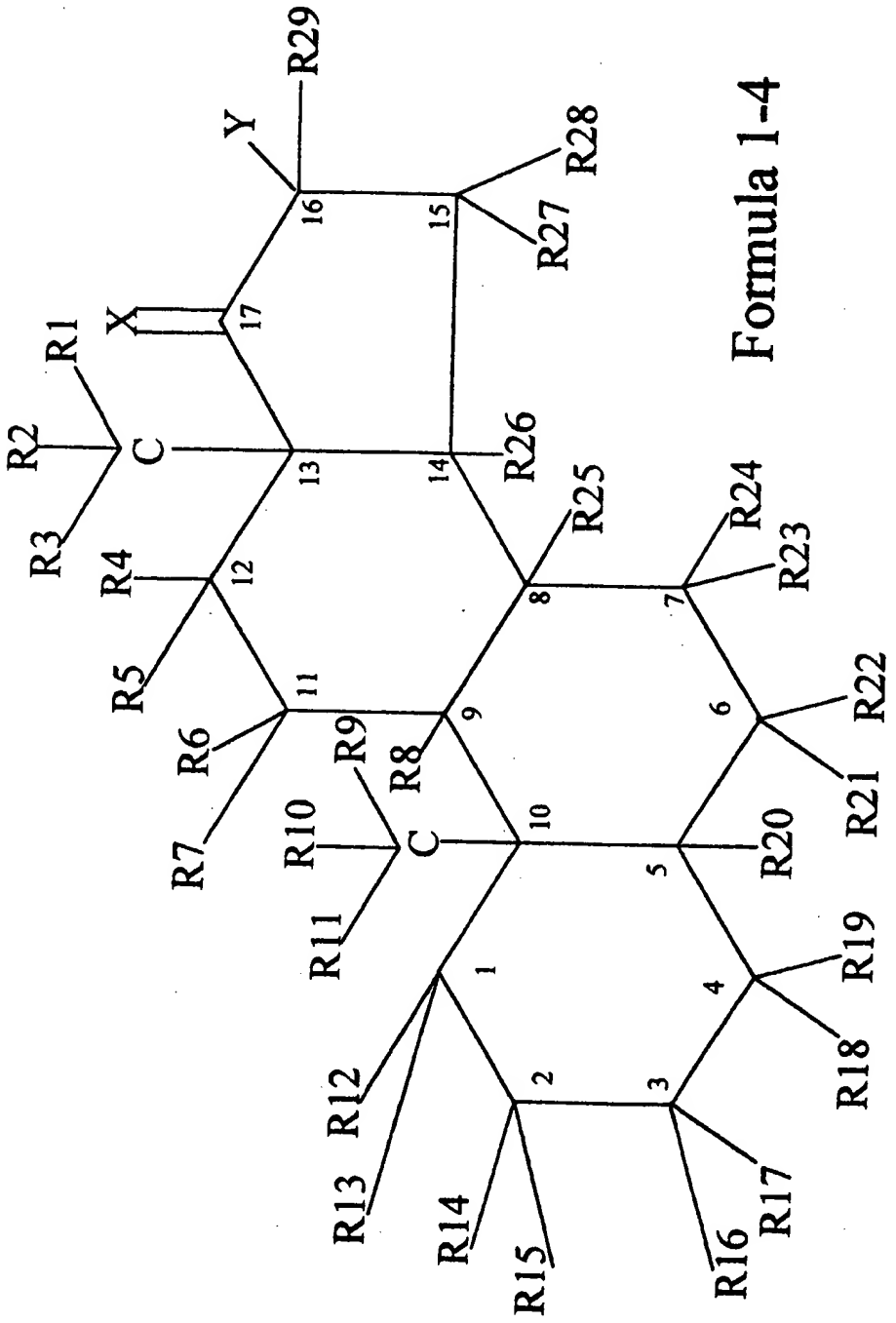
Formula 1-1

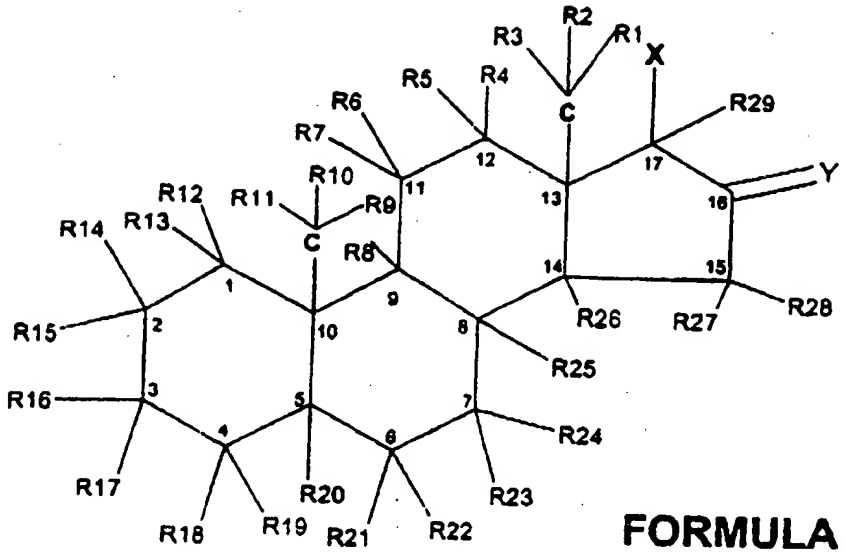

R30
R29
R28
R27
16
15
X
17
R1
R2
C
R3
13
14
R26
R25
R24
R23
R4
12
8
7
R5
11
9
6
R22
R6
R9
R8
R21
R7
R10
10
C
R20
5
R11
1
R19
4
R12
2
3
R18
R13
R14
R15
R16
R17

Formula 1-2

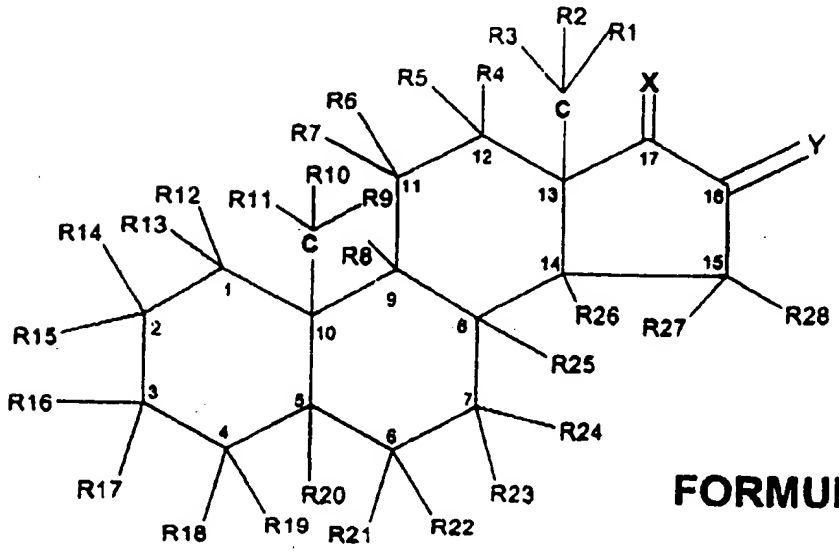

R29
Y
R28
R30
16
15
R27
X
17
R1
R2
C
13
14
R26
R3
R4
12
R25
R24
8
7
R23
R5
11
9
6
R22
R6
R9
R8
R21
R7
R10
C
10
5
R20
R11
1
4
R19
R12
2
3
R18
R13
R14
R15
R16
R17

Formula 1-3

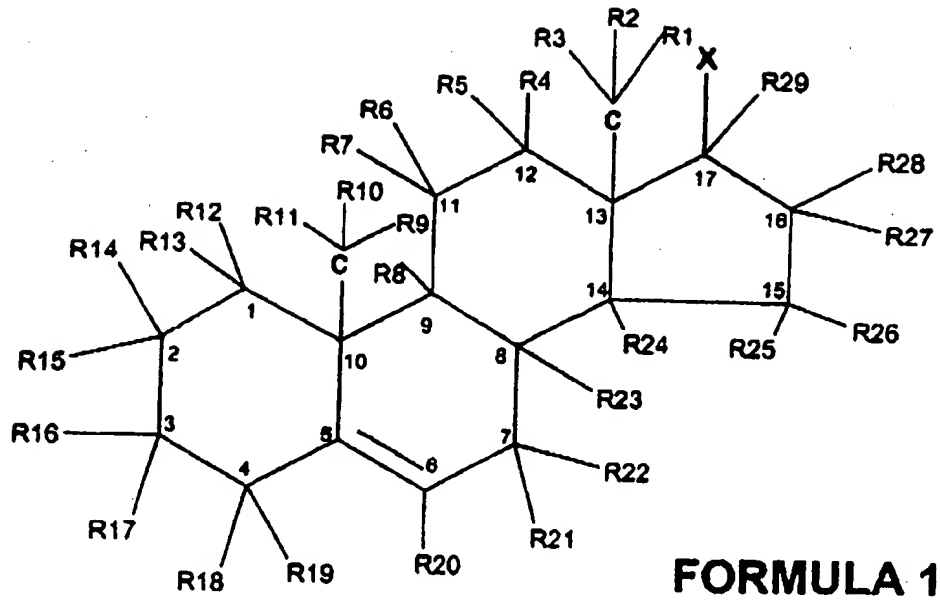

Formula 1-4
R29
Y
R28
R27
16
15
X
17
R1
R2
C
R3
13
14
R26
R25
R24
R4
12
8
7
R23
R5
11
9
6
R22
R6
R9
R8
R7
R10
10
C
R20
R21
5
R11
1
4
R19
R12
2
3
R18
R13
R14
R15
R16
R17



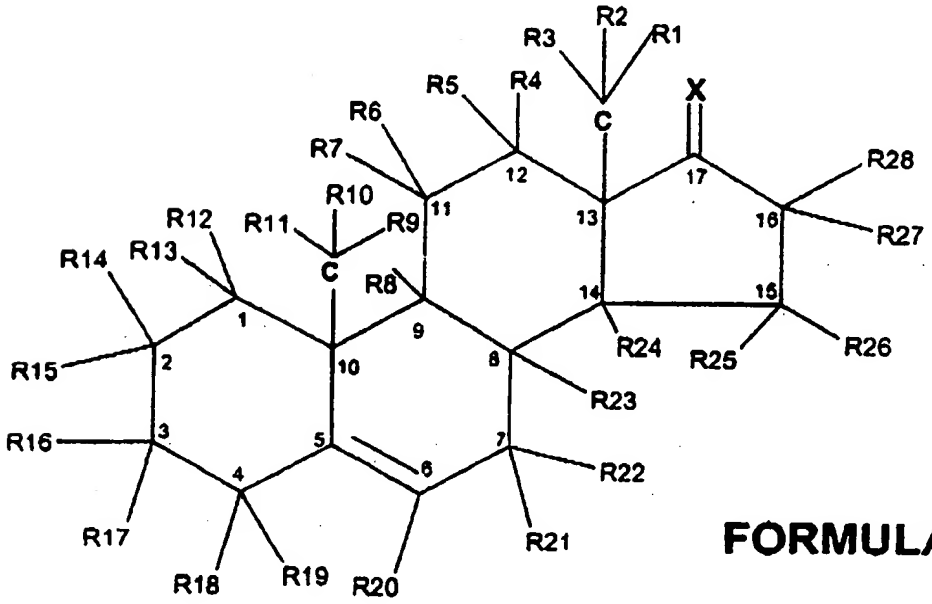
FORMULA 1-5



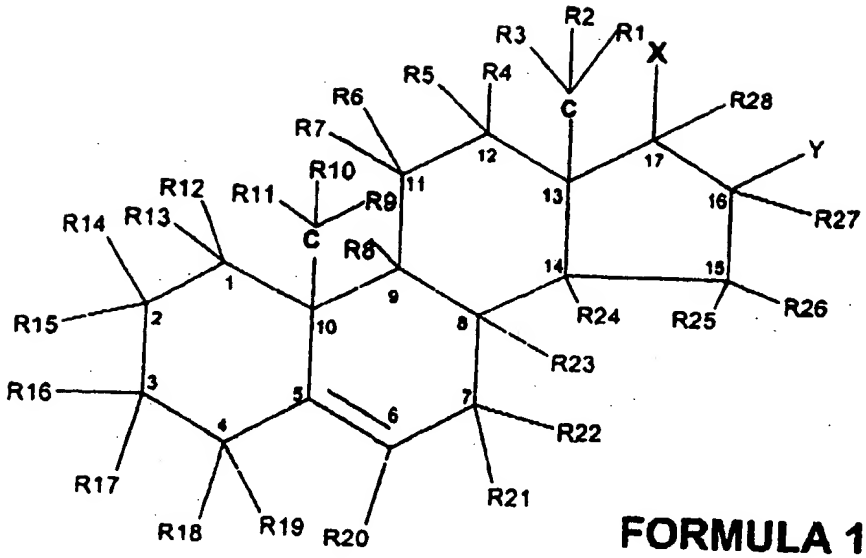
FORMULA 1-6



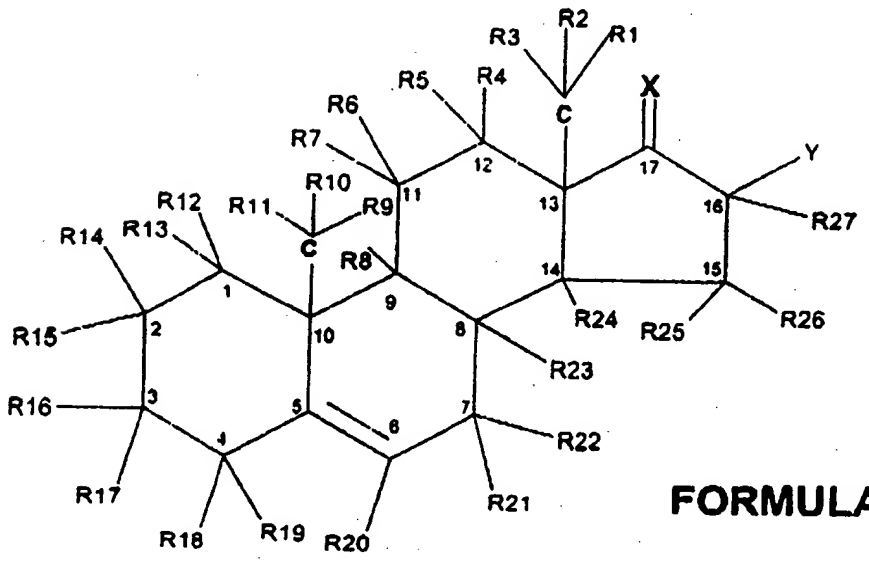
FORMULA 1-7



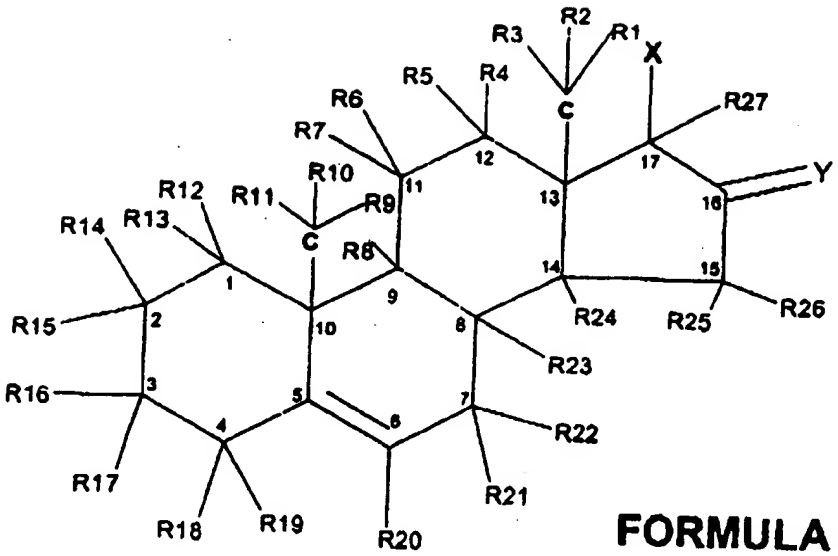
FORMULA 1-8



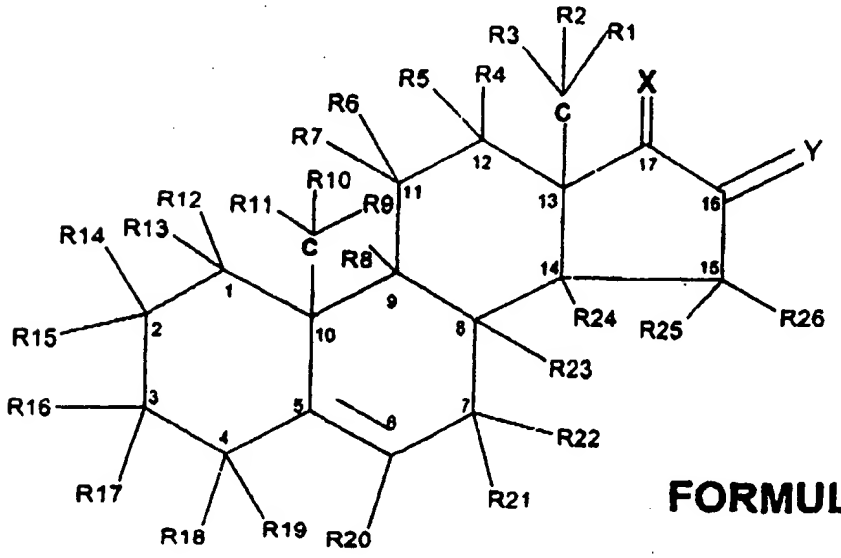
FORMULA 1-9



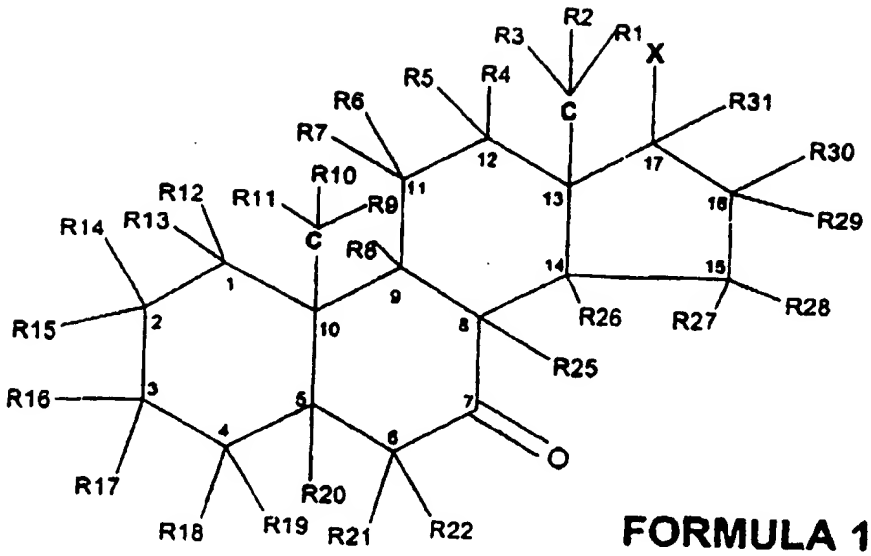
FORMULA 1-10



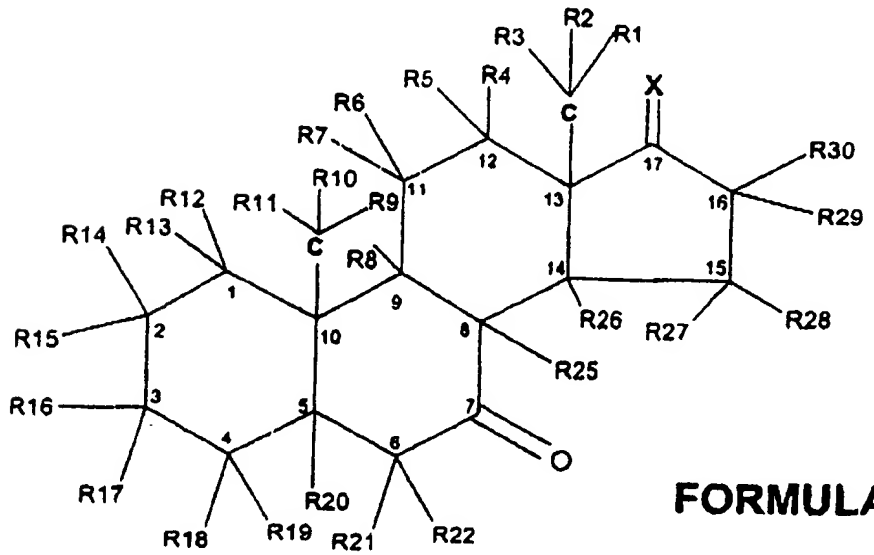
FORMULA 1-11



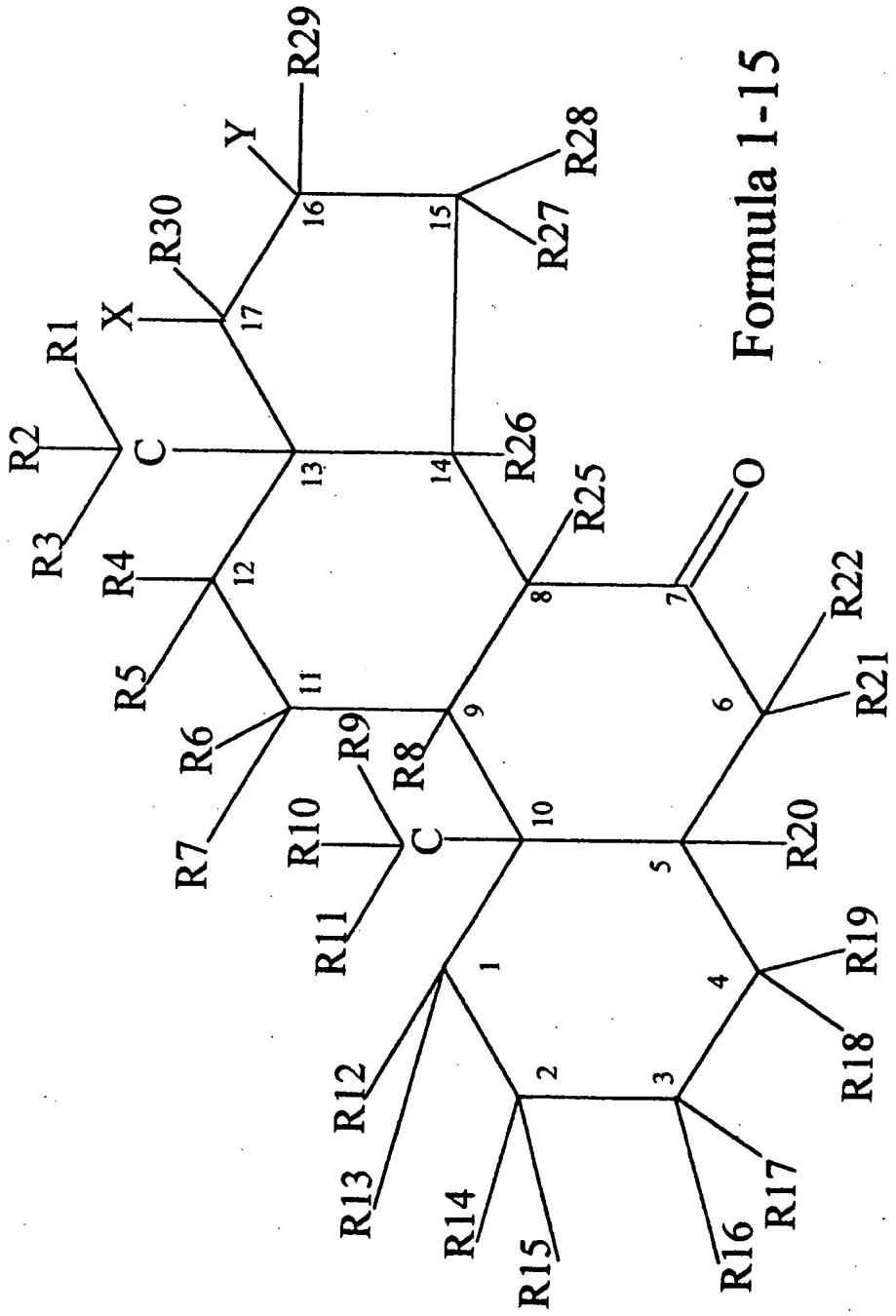
FORMULA 1-12

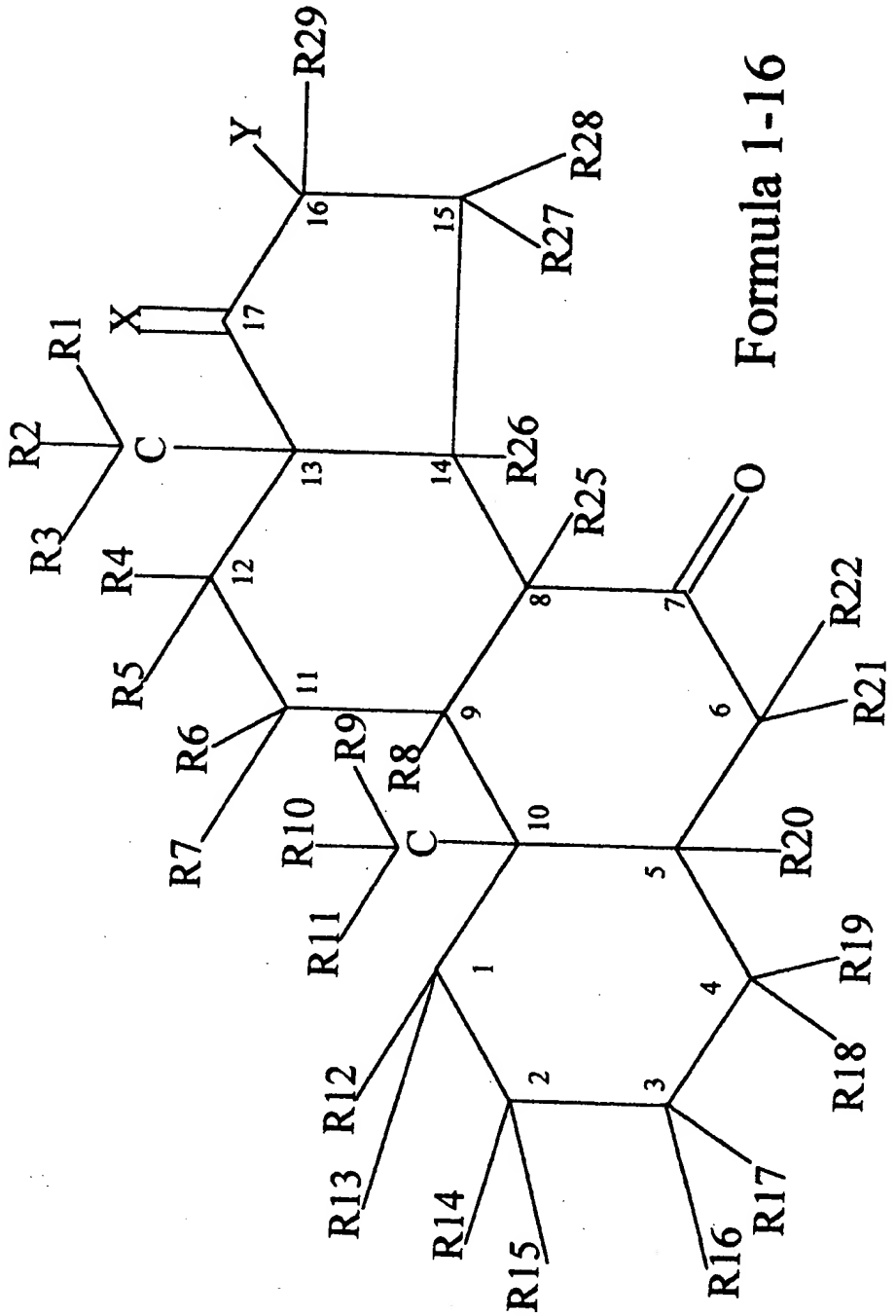


FORMULA 1-13

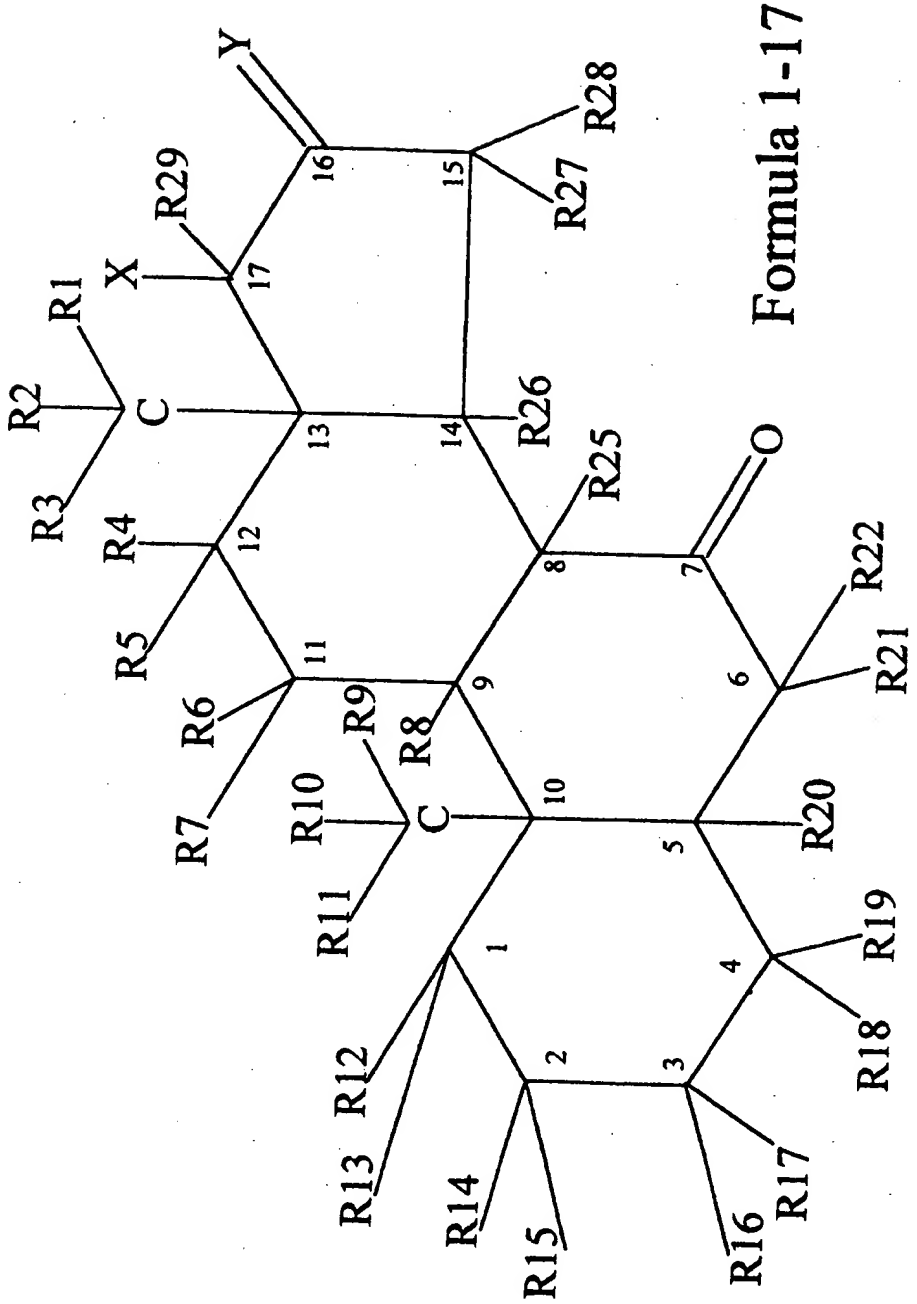


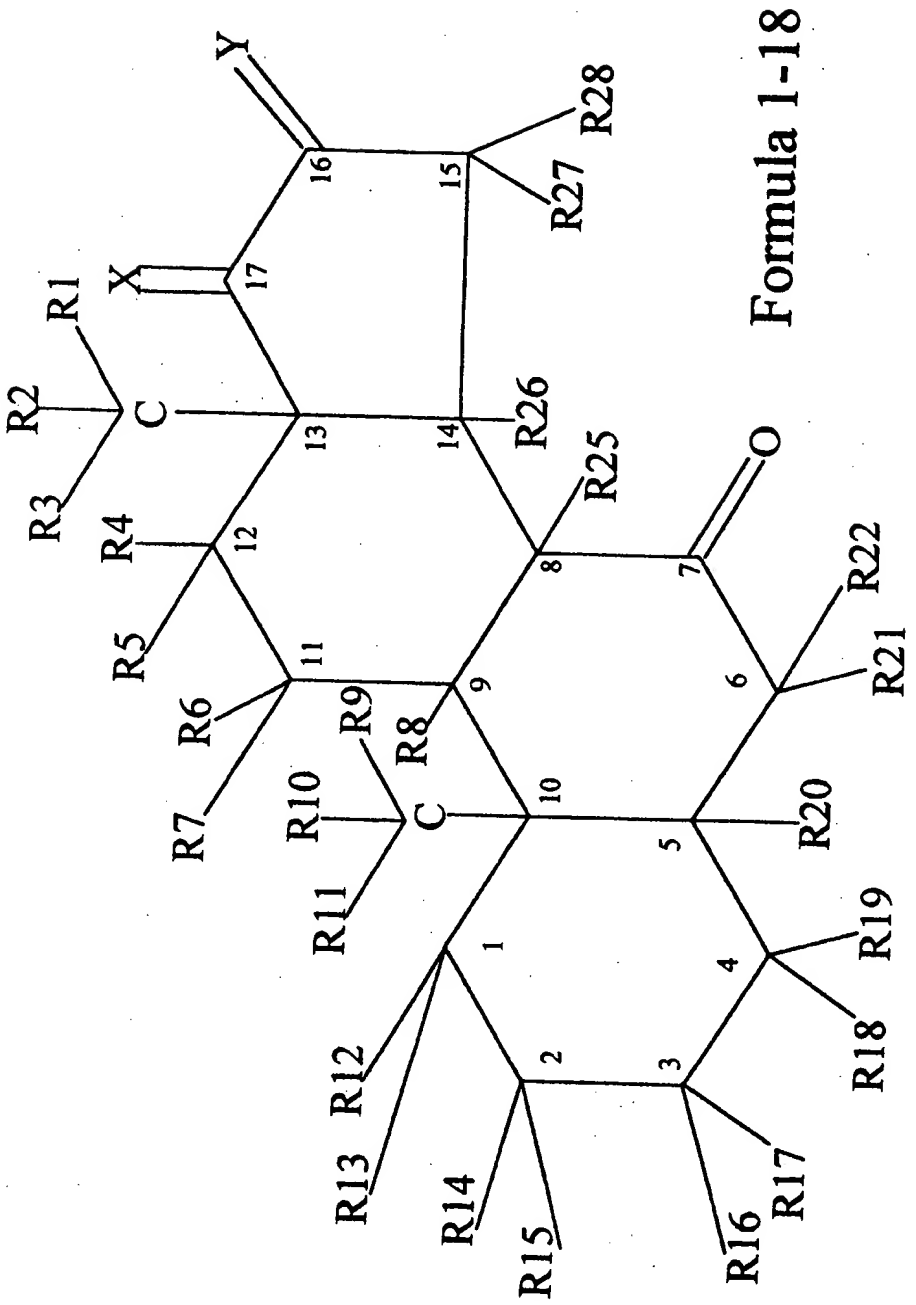
FORMULA 1-14

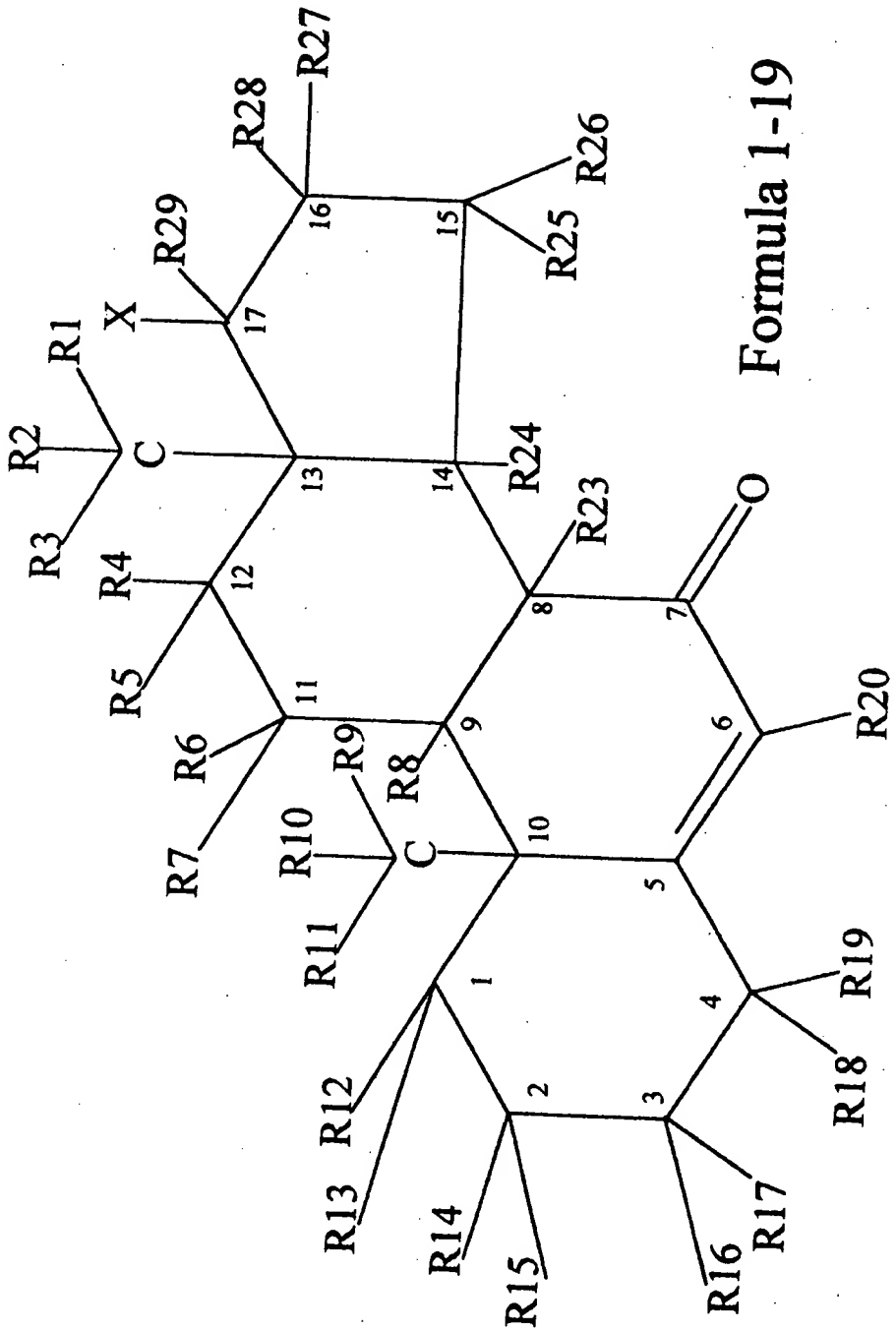

Formula 1-15
R29
Y
R28
R30
X
R27
R1
R2
C
R26
R3
R4
R25
O
R5
R22
R6
R9
R8
R21
R7
R10
C
R20
R11
R19
R12
R18
R13
R14
R17
R15
R16
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17


R29
Y
R28
R27
16
15
X
17
R1
R2
C
13
14
R26
R3
R4
12
R25
O
8
7
R5
11
9
6
R22
R21
R6
R9
R8
R7
R10
C
10
5
R20
R11
1
4
R19
R12
2
3
R18
R13
R14
R15
R16
R17

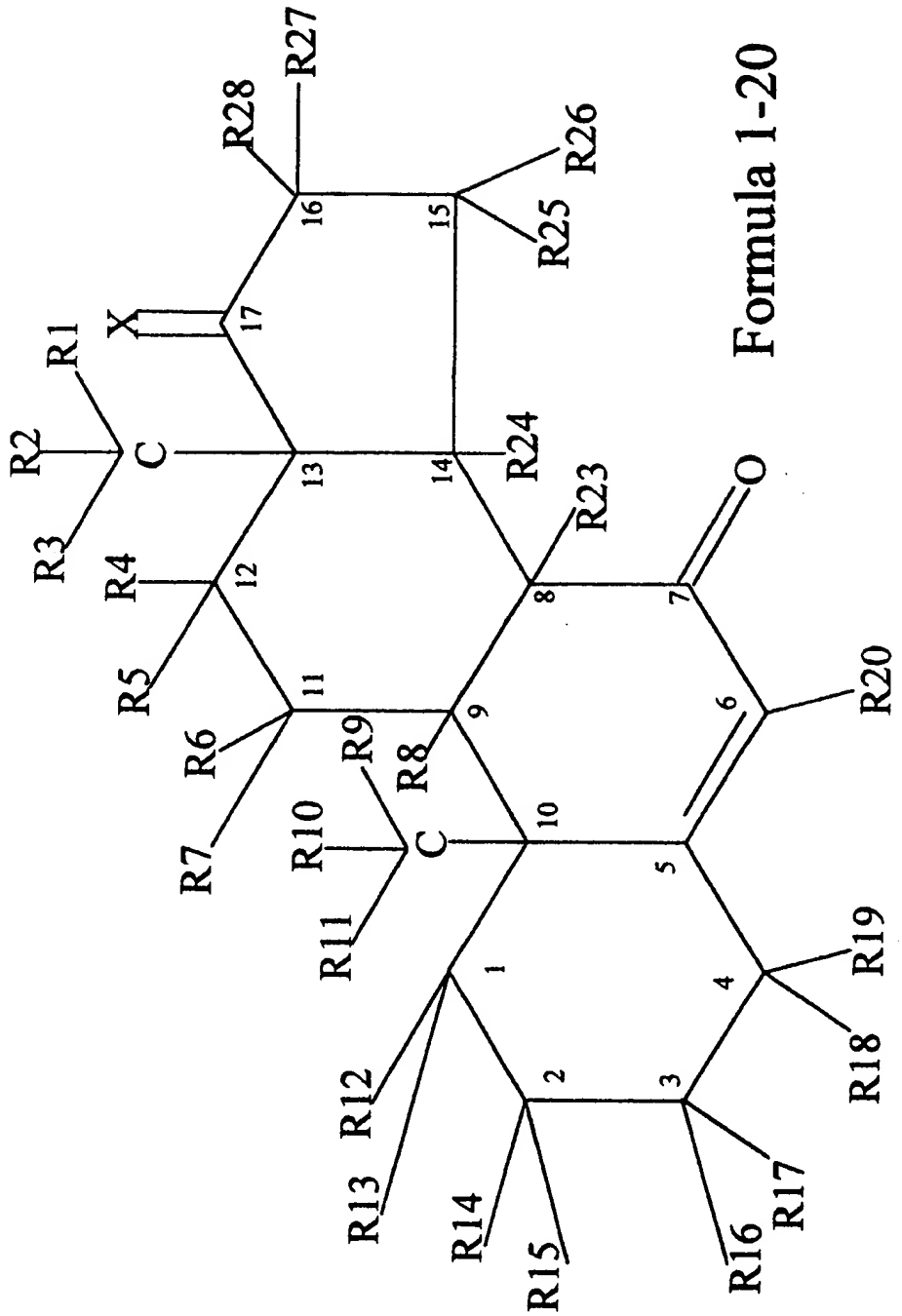
Formula 1-16

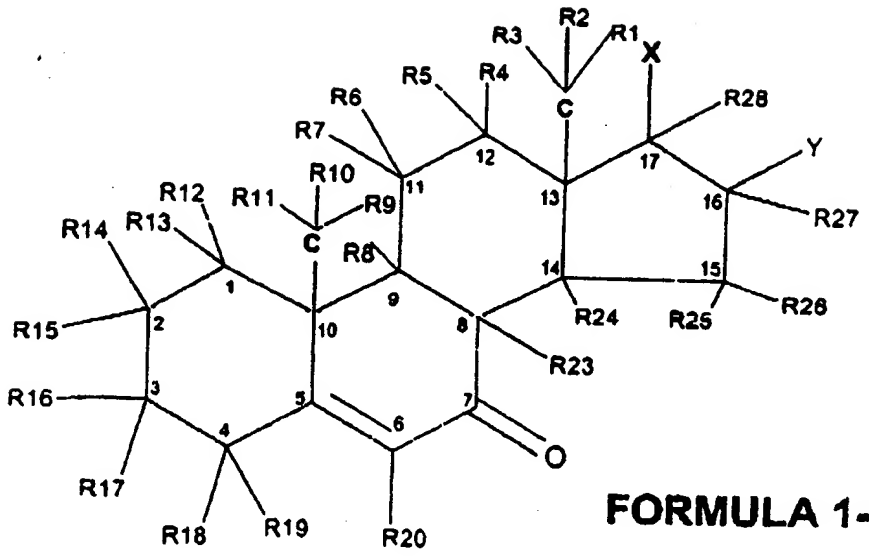

Formula 1-17
Y
R28
R27
R29
X
R1
R2
C
R3
R4
R5
R6
R7
R9
R8
R10
C
R11
R12
R13
R14
R15
R16
R17
R18
R19
R20
R21
R22
R25
R26
O
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17


Formula 1-18
Y
X
C
C
O
R1
R2
R3
R4
R5
R6
R7
R8
R9
R10
R11
R12
R13
R14
R15
R16
R17
R18
R19
R20
R21
R22
R25
R26
R27
R28
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

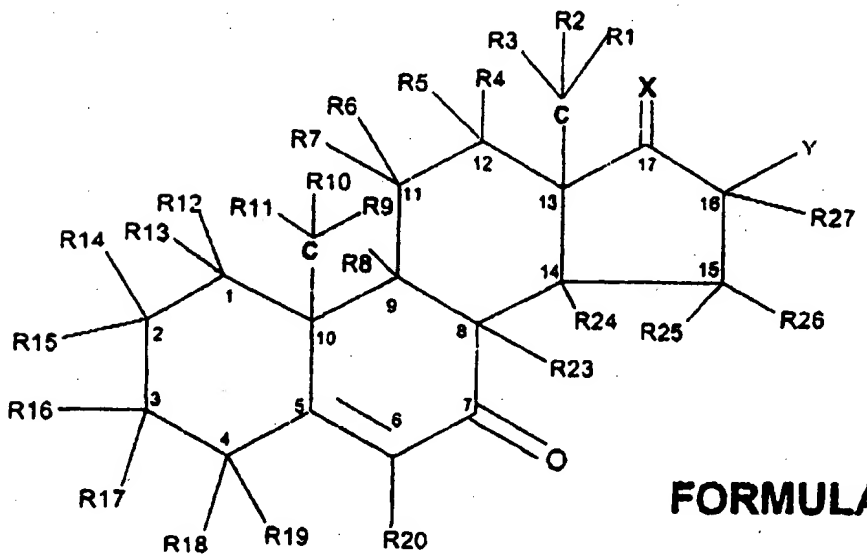

R27
R28
R26
R29
R25
X
R1
R2
C
R3
R24
R4
R23
O
R5
R20
R6
R9
R8
R7
R10
C
R11
R19
R12
R18
R13
R14
R17
R15
R16
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17

Formula 1-19

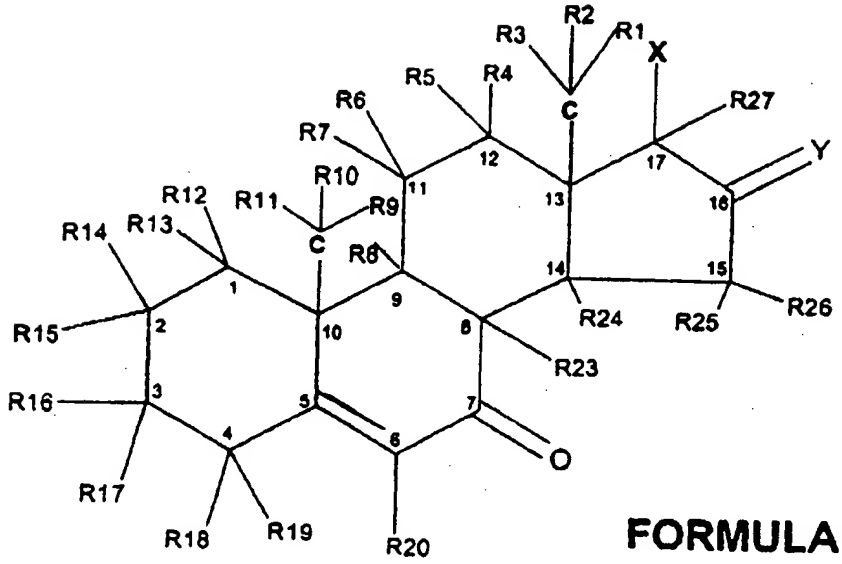

Formula 1-20
R1
R2
R3
C
X
R4
R5
R6
R7
R8
R9
R10
R11
C
R12
R13
R14
R15
R16
R17
R18
R19
R20
R23
R24
R25
R26
R27
R28
O
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17



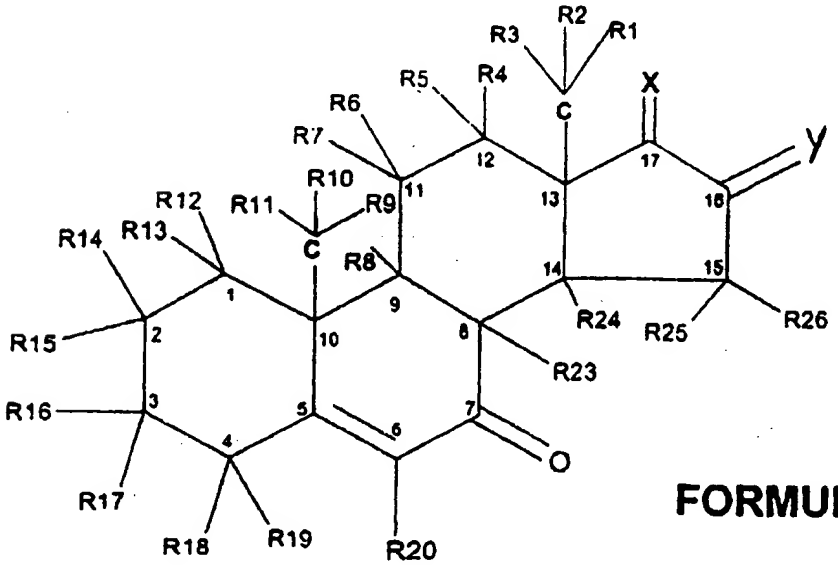
FORMULA 1-21



FORMULA 1-22



FORMULA 1-23



FORMULA 1-24

wherein:

X and Y (if present) are each independently selected from hydroxy, hydrogen, lower alkyl, CO_2R_{33} (i.e., - O - C(O)-R_{33} or - C(O) - O - R_{33}), halogen (such as Br, Cl, F or I), oxygen (double-bonded to the 16-position or 17-position carbon atom), and steroid molecule residue (residue B), wherein R_{33} is a straight or branched chain alkyl radical of 1 to 14 carbon atoms, said steroid molecule residue (residue B) having a structure corresponding to Formula I (with one hydrogen atom removed therefrom) and in which the moieties on residue B corresponding to positions X and Y (if present) are independently selected from halogen (e.g., Br, Cl, F or I), hydrogen, hydroxy, and CO_2R_{34}, wherein R_{34} is a straight or branched chain alkyl radical of 1 to 14 carbon atoms;

R_1 - R_{16} and R_{18} - R_{31}, if present, are each independently selected from hydrogen, halogen (such as Br, Cl, F or I), hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkyl and -S-CN;

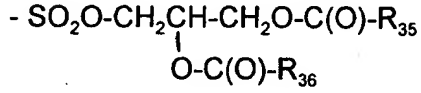
R_{17} is selected from hydrogen, hydroxy, halogen (such as Br, Cl, F or I), oxygen (double-bonded to the 3-position carbon atom), C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and OR_{32}, wherein R_{32} is selected from:

(a) SO_2OM, wherein M is selected from:

(i) hydrogen,

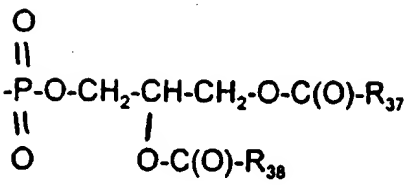
(ii) sodium,

(iii) sulphatide group having the formula:

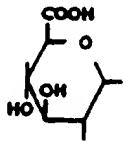


wherein R_{35} and R_{36} are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms

(iv) phosphatide group having the formula:

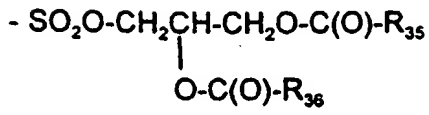


wherein R_{37} and R_{38} are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms or a glucuronide group having the formula



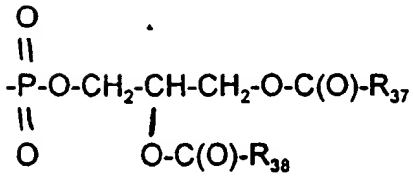
, and

(iii) sulphatide group having the formula:

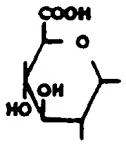


wherein R_{35} and R_{36} are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms

(iv) phosphatide group having the formula:

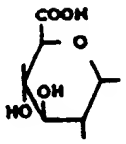


wherein R_{37} and R_{38} are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms or a glucuronide group having the formula

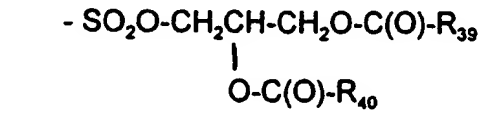


, and

(v) glucuronid group having the formula:

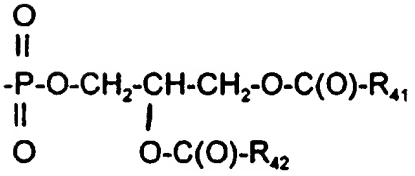


(b) sulphatide group having the formula:

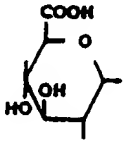


wherein R_{39} and R_{40} are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms

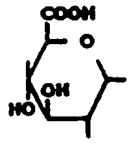
(c) phosphatide group having the formula:



wherein R_{41} and R_{42} are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms or a glucuronide group having the formula



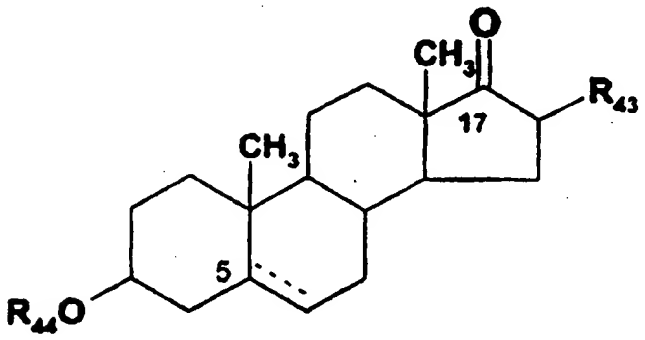
(d) glucuronide group having the formula:



(e) C_1 - C_{18} fatty acid, C_{1-10} acetylenic, $(J)_n$-phenyl-C_{1-5}-alkyl or $(J)_n$-phenyl-C_{1-5}-alkenyl, where n is 0, 1, 2 or 3, and each J is independently selected from halogen, C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkoxy, carboxy, nitro, sulfate, sulfonyl, C_{1-6} carboxylesters or C_{1-6} sulfate esters.

, and metabolites, analogs and precursors thereof, and pharmaceutically acceptable salts of any such compounds, metabolites, analogs and precursors. Persons of skill in the art can readily determine whether any particular compound is such a compound, or such an analog, precursor or metabolite thereof, or pharmaceutically acceptable salt thereof.

In a preferred aspect, the anti-viral agent is selected from among compound having the following formula 1 - 25 (and precursors, metabolites and analogs ther of):



wherein

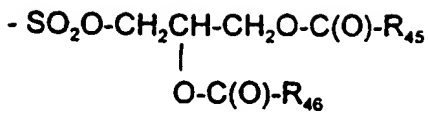
R_{43} is a hydrogen atom or bromine atom, and

R_{44} is:

-a hydrogen atom,

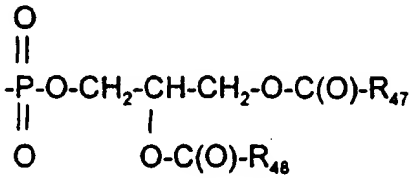
-an SO_2OM group (wherein M is a hydrogen atom or a sodium atom),

-a sulphatide group having the formula

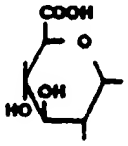


wherein R_{45} and R_{46} are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms

-a phosphatide group having the formula



wherein R_{47} and R_{48} are each independently selected from straight or branched chain alkyl radical of 1 to 14 carbon atoms or a glucuronide group having the formula



,or

-a glucuronide group having the formula

Preferably in the compound of formula 1 - 25, R_{43} and R_{44} are each hydrogen. An especially preferred compound is dehydroepiandrosterone (DHEA) wherein R_{43} and R_{44} are each hydrogen and the double bond is present. In a further embodiment of the invention, the compound is epiandrosterone wherein R_{43} and R_{44} are each hydrogen and the double bond is absent. This unsaturated 5-position steroid can also be prepared as an anti-viral agent wherein the R_{43} position is occupied by any of the following halogens (bromine, chlorine, fluorine, iodine). In a further embodiment of the invention, the compuond is 16α-bromoepiandrosterone, wherein R_{43} is Br, R_{44} is H and the double bond is absent. In a still further embodiment of the invention, the compound is according to formula I - 25, wherein R_{43} is Br, R_{44} is H and the double bond is not present (i.e., where the dotted line is shown in formula I - 25, there is a single bond). Other preferred compounds are dehydroepiandrosterone sulphate, wherein R_{43} is H, R_{44} is SO_2-OM and M is as hereinbefore defined and the double bond is present, and 5β-androstan-3β-ol-17-one.

As defined above, the compound of Formula 1 may also be dehydroepiandrosterone sulphatides, phosphatides, or glucuronide wherein a hydrogen atom is attached to the carbon atom at the 16-position, and R_{17} is a sulphatide, phosphatide, or glucuronide group as hereinabove defined, and the double bond between the carbon atoms at the 5-position and the 6-position is present. In particular, when R_{17} is not hydrogen, the compounds may be DHEA conjugates such as hexyl sulfate, dodecyl sulfate, octadecyl sulfate, octadecanoylglycol sulfate, O-dihexadecylglycerol sulfate, hexadecane sulfonate, dioctadecanoylglycerol phosphate, or O-hexadecylglycerol phosphate.

The compounds of Formula 1 can exist in a polymorph form.

Other preferred anti-viral agents include protease inhibitors.

Protease inhibitors are drugs that resemble pieces of the protein chain that protease normally cuts. By "gumming up" the protease "scissors," HIV protease inhibitors prevent protease from cutting long chains of proteins and enzymes into the shorter pieces that HIV needs to make new copies of itself.

New copies of HIV are still made and still push through the wall of the infected cell even if the long chains are not cut up into the correct smaller pieces. But these new copi s of HIV are "defective", in that they cannot go on to infect other cells.

Protease inhibitors can greatly reduce the number of new, infectious copies of HIV made inside cells. If protease inhibitors succeed in making most new HIV viruses defective, HIV infection would not spread inside the body as quickly as it does now. The European name for protease inhibitor is proteinase inhibitor.

A protease inhibitor alone will generally not get rid of HIV in an infected person's body. Even though these drugs can reduce the amount of virus, more virus can remain elsewhere in the body. Because some infected cells are "dormant" or "latently infected" – meaning they are already infected but still waiting to make new virus – many researchers doubt that any one drug can remove all the virus in an infected person, believing that some virus will stay in the body in latently infected cells. Herein is described, as can be observed from bloodwork obtained according to this invention, the use of agonist to Th_2 cytokine, specifically IL-10, to cause viral replication. See treatment A in Figures 3(A), 3(B), 3(C) and 3(D) wherein due to viral replication, fewer latent virus are present.

Even so, if protease inhibitors do slow the pace at which HIV makes new copies of itself, fewer new cells would be infected by HIV, and cells already infected would eventually die. As a result, because there is less virus, fewer CD4 cells would be infected, fewer would be destroyed, and an HIV-infected person could stay healthier longer. So controlling the amount of virus would help a person fight off other infections longer and continue to live an active life.

The main ways protease inhibitors differ from the other anti-HIV drugs used now are in their target and in their strength. These other drugs are called reverse transcriptase inhibitors because they disturb the job of an HIV enzyme called reverse transcriptase. Reverse transcriptase is the enzyme HIV uses to change its chemical (or genetic) message into a form that can easily be inserted inside the nucleus of the infected cell.

This step in the HIV replication process happens soon after HIV infects a cell – much earlier than the step in which protease inhibitors are involved. Because protease inhibitors and reverse transcriptase inhibitors work at two separate steps in the HIV replication process, some studies are testing the use of drugs from both groups at the same time to treat HIV infection.

Protease inhibitors also differ from reverse transcriptase inhibitors in their

strength. Results from laboratory tests and tests in people show that certain protease inhibitors are many times more powerful than reverse transcriptase inhibitors in slowing the replication of HIV and in increasing the number of CD4 cells in the body.

Protease Inhibitors

Drug name(s)	Maker
Invirase (saquinavir, RO-31-8959)	Hoffmann-La Roche
Norvir (ritonavir, ABT-538)	Abbott
Crixivan (indinavir, MK-639)	Merck
Viracept (nelfinavir, AG-1343)	Agouron
VX-478 141W94	Glaxo-Wellcome/Vertex
KNI-272 (kynostatin)	Nikko Kyoto Pharmaceutical and National Cancer Institute
U-103373	Upjohn
CGP-53437	Ciba-Geigy
Hoe/Bay-793	Hoechst-Bayer
SR-41476	Sanofi

HIV can become resistant to two or more drugs at the same time. When it does, HIV is said to be cross-resistant to those drugs. Researchers studying the protease inhibitor indinavir found that HIV in some people first became resistant to the drug and then became resistant to several other protease inhibitors when they were tested later.

Other preferred anti-viral agents include reverse transcriptase inhibitors.

In the United States, physicians may prescribe five reverse transcriptase inhibitors. The common names of these drugs are:

AZT (Retrovir, zidovudine)

ddI (Videx, didanosine)

ddC (Hivid, zalcitabine)

d4T (Zerit, stavudine)

3TC (Epivir, Lamivudine)

In preferred embodiments of the present invention, there are provided compositions which include one or more Interleukin-4 receptor. Additionally, preferred embodiments of the present invention relate to a combination therapy for the treatment of viral infection containing (a) an Interleukin-4 receptor in combination with (b) an anti-viral agent.

Interleukin-4 (IL-4, also known as B-cell stimulating factor, or BSF-1) was originally characterised by its ability to stimulate the proliferation of B-cells in response to low concentrations of antibodies directed to surface immunoglobulin. More recently, IL-4 has been shown to possess a far broader spectrum of biological activities, including growth co-stimulation of T-cells, mast cells, granulocytes, megakaryocytes, and erythrocytes. In addition, IL-4 stimulates the proliferation of several IL-2 and IL-3 (Interleukin-3) dependent cell lines, induces the expression of class II major histocompatibility complex molecules on resting B-cells, and enhances the secretion of IgE and IgG1 isotypes by stimulated B-cells. Both murine and human IL-4 have been definitively characterised by recombinant DNA technology and by purification to homogeneity of the natural murine protein (Yokota et al., Proc. Natl. Acad. Sci. USA 83:5894, 1986; Norma et al., Nature 319:640, 1986; and Grabstein et al., J. Exp. Med. 163:1405, 1986).

The biological activities of IL-4 are mediated by specific cell surface receptors for IL-4 which are expressed on primary cells and in vitro cell lines of mammalian origin. IL-4 binds to the receptor, which then transduces a biological signal to various immune effector cells. Purified IL-4 receptor (IL-4R) compositions will therefore be useful in diagnostic assays for IL-4 or IL-4 receptor, and in raising antibodies to IL-4 receptor for use in diagnosis or therapy. In addition, purified IL-4 receptor compositions may be used directly in therapy to bind or scavenge IL-4, providing a means for regulating the biological activities of this cytokine.

As used herein, the terms "IL-4 receptor" or IL-4R" refer to proteins which bind Interleukin-4 (IL-4) molecules and, in their native configuration as intact human plasma membrane proteins, play a role in transducing the biological signal provided by IL-4 to

a cell. Intact receptor proteins generally include an extracellular region which binds to a ligand, a hydrophobic transmembrane region which causes the protein to be immobilised within the plasma membrane lipid bilayer, and a cytoplasmic or intracellular region which interacts with cytoplasmic proteins and/or chemicals to deliver a biological signal to effector cells via a cascade of chemical reactions within the cytoplasm of the cell. The hydrophobic transmembrane region and a highly charged sequence of amino acids in the cytoplasmic region immediately following the transmembrane region co-operatively function to halt transport of the IL-4 receptor across the plasma membrane.

"IL-4 receptors" are proteins having amino acid sequences which are substantially similar to the native mammalian Interleukin-4 receptor amino acid sequences disclosed in Fig. 1 (SEQ ID NO. 1) (i.e., Figs. 1A, 1B, 1C), and Fig. 2 (SEQ ID NO. 2) (i.e., Figs. 2A, 2B, 2C and 2D), or fragments thereof, and which are biologically active as defined below, in that they are capable of binding Interleukin-4 (IL-4) molecules or transducing a biological signal initiated by an IL-4 molecule binding to a cell, or cross-reacting with anti-IL-4R antibodies raised against IL-4R from natural (i.e., nonrecombinant) sources. The native human IL-4 receptor molecule has an apparent molecular weight by SDS-PAGE of about 140 kilodaltons (kDa). The native murine IL-4 receptor molecule has an apparent molecular weight by SDS-PAGE of about 140 kilodaltons (kDa). The terms "IL-4 receptor" or "IL-4R" include, but are not limited to, soluble IL-4 receptors, as defined below. Specific IL-4 receptor polypeptides are designated herein by parenthetically indicating the amino acid sequence numbers, followed by any additional amino acid sequences. As used throughout the specification, the term "mature" means a protein expressed in a form lacking a leader sequence as may be present in full-length transcripts of a native gene. Various bioequivalent protein and amino acid analogs are described in the detailed description of the invention.

"Substantially similar" IL-4 receptors include those whose amino acid or nucleic acid sequences vary from the native sequences by one or more substitutions, deletions, or additions, the net effect of which is to retain biological activity of the IL-4R protein. For example, nucleic acid subunits and analogs are "substantially similar" to the specific DNA sequences disclosed herein if: (a) the DNA sequence is derived from the coding region of a native mammalian IL-4R gene; (b) the DNA sequence is capable of

hydrodisation to DNA sequences of (a) under moderately stringent conditions and which encode biologically active IL-4R molecules; or DNA sequences which are degenerate as a result of the genetic code to the DNA sequences defined in (a) or (b) and which encode biologically active IL-4R molecules. Substantially similar analog proteins will generally be greater than about 30 percent similar to the corresponding sequence of the native IL-4R. Sequences having lesser degrees of similarity but comparable biological activity are considered to be equivalents. More preferably, the analog protein will be greater than about 70 percent similar to the corresponding sequence of the native IL-4R, in which case they are defined as being "substantially identical". In defining nucleic acid sequences, all subject nucleic acid sequences capable of encoding substantially similar amino acid sequences are considered substantially similar to a reference nucleic acid sequence. Percent similarity may be determined, for example, by comparing sequence information using the GAP computer program, version 6.0, available from the University of Wisconsin Genetics Computer Group (UWGCG). The GAP program utilises the alignment method of Needleman and Wunsch (J. Mol. Biol. 48: 443, 1970), as revised by Smith and Waterman (Adv. Appl Math.2:482, 1981). Briefly, the GAP program defines similarity as the number of aligned symbols (i.e., nucleotides or amino acids) which are similar, divided by the total number of symbols in the shorter of the two sequences. The preferred default parameters for the GAP program include: (1) a unary comparison matrix (containing a value of 1 for identities and 0 for non-identies) for nucleotides) for nucleotides, and the weighted comparison matrix of Gribskov and Burgess, Nucl. Acids Res. 14:6745, 1986, as described by Schwartz and Dayhoff, ed., Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, pp. 353-358, 1979; (2) a penalty of 3.0 for each gap and an additional 0.10 penalty for each symbol in each gap; and (3) no penalty for end gaps.

"Soluble IL-4 receptor" or "sIL4-R" as used in the context of the present invention refers to a protein, or a substantially equivalent analog, having an amino acid sequence corresponding to the extracellular region of native IL-4 receptors, for example, polypeptides having the amino acid sequences substantially equivalent to the sequences of amino acids 1-208 of Fig. 1A (part of SEQ ID NO. 1), amino acids 1-207 of Fig. 2A (part of SEQ ID NO. 2). Equivalent sIL-4Rs include polypeptides which vary

from the sequences shown in Figs. 1 or 2 (SEQ ID NOS. 1 and 2) by one or more substitutions, deletions, or additions, and which retain the ability to bind IL-4 and inhibit the ability of IL-4 to transduce a signal via cell surface bound IL-4 receptor proteins. Because sIL-4R proteins are devoid of a transmembrane region, they are secreted from the host cell in which they are produced. When administered in therapeutic formulations, sIL-4R proteins circulate in the body and bind to circulating IL-4 molecules, preventing interaction of IL-4 with natural IL-4 receptors and inhibiting transduction of IL-4 mediated biological signals, such as immune or inflammatory responses. The ability of a polypeptide to inhibit IL-4 signal transduction can be determined by transfecting cells with recombinant IL-4 receptor DNAs to obtain recombinant receptor expression. The cells are then contacted with IL-4 and the resulting metabolic effects examined. If an effect results which is attributable to the action of the ligand, then the recombinant receptor has signal transducing activity. Exemplary procedures for determining whether a polypeptide has signal transducing activity are disclosed by Idzerda et al., J. Exp. Med., March 1990 in press, Curtis et al., Proc. Natl. Acad. Sci. USA 86: 3045 (1989), Prywes et al., EMBO J. 5:2179 (1986) and Chou et al., J. Biol. Chem. 262:1842 (1987). Alternatively, primary cells of cell lines which express an endogenous IL-4 receptor and have a detectable b\iological response to IL-4 could also be utilised. Such is the case with the CTLL-2 cell line which responds by short term proliferation in response to either IL-2 or IL-4; the IL-4 induced proliferation can be blocked specifically by the addition of exogenous soluble IL-4R (Mosley et al., Cell 59:335 (1989). In addition, any one of the in vivo or in vitro assays described in Examples 1-10 can be utilised to determine whether a soluble IL-4R inhibits transduction of a specific IL-4 mediated biological signal. The cloning, sequencing and expression of full-length and soluble forms of the receptor for murine IL-4 have recently been described by Mosley et al., Cell 59:335, 1989.

"Recombinant," as used herein, means that a protein is derived from recombinant (e.g., microbial or mammalian) expression systems. "Microbial" refers to recombinant proteins made in bacterial or fungal (e.g., yeast) expression systems. As a product, "recombinant microbial" defines a protein produced in a microbial expression system which is essentially free of native endogenous substances. Protein expressed in most bacterial cultures, e.g., E. coli, will be free of glycan. Protein expressed in yeast

may have a glycosylation pattern different from that expressed in mammalian cells.

"Biologically active," as used throughout the specification, e.g., as a characteristic of IL-4 receptors, means that a particular molecule shares suffici nt amino acid sequence similarity with the embodiments of the present invention disclosed herein to be capable of binding detectable quantities of IL-4, transducing an IL-4 signal to a cell, for example, as a component of a hybrid receptor construct, or cross-reacting with anti-IL-4R antibodies raised against IL-4R from natural (i.e., nonrecombinant) sources. Preferably, biologically active IL-4 receptors within the scope of the present invention are capable of binding greater than 0.1 nmoles IL-4 per nmole receptor, and most preferably, greater than 0.5 nmole IL-4 per nmole receptor in standard binding assays (see below).

"DNA sequence" refers to a DNA molecule, in the form of a separate fragment or as a component of a larger DNA construct, which has been derived from DNA isolated at least once in substantially pure form, i.e., free of contaminating endogenous materials and in a quantity or concentration enabling identification, manipulation, and recovery of the sequence and its component nucleotide sequences by standard biochemical methods, for example, using a cloning vector. Such sequences are preferably provided in the form of an open reading frame uninterrupted by internal nontranslated sequences, or introns, which are typically present in eukaryotic genes. Genomic DNA containing the relevant sequences could also be used. Sequences of non-translated DNA may be present 5' or 3' from the open reading frame, where the same do not interfere with manipulation or expression of the coding regions.

"Nucleotide sequence" refers to a heteropolymer of deoxyribonucleotides. DNA sequences encoding the proteins provided by this invention can be assembled from cDNA fragments and short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic gene which is capable of being expressed in a recombinant transcriptional unit.

"Recombinant expression vector" refers to a replicable DNA construct used either to amplify or to express DNA which encodes IL-4R and which includes a transcriptional unit comprising an assembly of (1) a genetic element or elements having a regulatory role in gene expression, for example, promoters or enhancers, (2) a structural or coding sequence which is transcribed into mRNA and translated into

protein, and (3) appropriate transcription and translation initiation and termination sequences. Structural elements intended for use in yeast expression systems preferably include a leader sequence enabling extracellular secretion of translated protein by a host cell. Alternatively, where recombinant protein is expressed without a leader or transport sequence, it may include an N-terminal methionine residue. This residue may optionally be subsequently cleaved from the expressed recombinant protein to provide a final product.

"Recombinant microbial expression system" means a substantially homogenous monoculture of suitable host micro-organisms, for example, bacteria such as E. coli or yeast such as S. cerevisiae, which have stably integrated a recombinant transcriptional unit into chromosomal DNA or carry the recombinant transcriptional unit as a component of a resident plasmid. Generally, cells constituting the system are the progeny of a single ancestral transformant. Recombinant expression systems as defined herein will express heterologous protein upon induction of the regulatory elements linked to the DNA sequence or synthetic gene to be expressed.

The present invention provides substantially homogeneous recombinant mammalian IL-4R polypeptides substantially free of contaminating endogenous materials and, optionally, without associated native-pattern glycosylation. The native murine and human IL-4 receptor molecules are recovered from cell lysates as glycoproteins having an apparent molecular weight by SDS-PAGE about 130-145 kilodaltons (kDa). Mammalian IL-4R of the present invention include, by way of example, primate, human, murine, canine, feline, bovine, ovine, equine and porcine IL-4R. Derivatives of IL-4R within the scope of the invention also include various structural forms of the primary protein which retain biological activity. Due to the presence of ionisable amino and carboxyl groups, for example, an IL-4R protein may be in the form of acidic or basic salts, or in neutral form. Individual amino acid residues may also be modified by oxidation or reduction.

The primary amino acid structure may be modified by forming covalent or aggregative conjugates with other chemical moieties, such as glycosyl groups, lipids, phosphate, acetyl groups and the like, or by creating amino acid sequence mutants. Covalent derivatives are prepared by linking particular functional groups to IL-4R amino acid side chains or at the N- or C-termini. Other derivatives of IL-4R within the scope

of this invention include covalent or aggregative conjugates of IL-4R or its fragments with other proteins or polypeptides, such as by synthesis in recombinant culture as N-terminal or C-terminal fusions. For example, th conjugated peptide may be a signal (or leader) polypeptide sequence at the N-terminal region of the protein which co-translationally or post-translationally directs transfer of the protein from its site of synthesis to its site of function inside or outside of the cell membrane or wall (e.g., the G-factor leader). IL-4R protein fusions can comprise peptides added to facilitate purification or identification of IL-4R (e.g., poly-His). Specific examples of a poly-HIS fusion construct that is biologically active are soluble human IL-4R (1-207) His His and soluble human IL-4R (1-207) His His His His His His (SEQ ID NO. 3). The amino acid sequence of IL-4 receptor can also be linked to the peptide Asp-Tyr-Lys-Asp-Asp-Asp-Asp-Lys (DYKDDDDK) (SEQ ID NO. 4) (Hopp et al., Bio/Technology 6:1204, 1988) The latter sequence is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody, enabling rapid assay and facile purification of expressed recombinant protein. This sequence is also specifically cleaved by bovine mucosal enterokinase at the residue immediately following the Asp-Lys pairing. Fusion proteins capped with this peptide may also be resistant to intracellular degradation in E. coli. A specific example of such a peptide is soluble human IL-4R (1-207) Asp Tyr Lys Asp Asp Asp Asp Lys (SEQ ID NO. 3).

IL-4R derivatives may also be used as immunogens, reagents in receptor-based immunoassay, or as binding agents for affinity purification procedures of IL-4 or other binding ligands. IL-4R derivatives may also be obtained by cross-linking agents, such as M-maleimidobenzoyl succinimide ester and N-hydroxysuccinimide, at cysteine and lysine residues. IL-4R proteins may also be covalently bound through reactive side groups to various insoluble substrates, such as cyanogen bromide-activated, bisoxirane-activated, carbonyldiimidazole-activated or tosyl-activated agarose structures, or by adsorbing to polyolefin surfaces (with or without glutaraldehyde cross-linking). Once bound to a substrate, IL-4R may be used to selectively bind (for purposes of assay or purification) anti-IL-4R antibodies or IL-4.

The present invention also includes IL-4R with or without associated native-pattern glycosylation. IL-4R expressed in yeast or mammalian expression systems, e.g., COS-7 cells, may be similar or significantly different in molecular weight and

glycosylation pattern than the native molecules, depending upon the expression system. Expression of IL-4R DNAs in bacteda such as E. coli provides non-glycosylated molecules. Functional mutant analogs of mammalian IL-4R having inactivated N-glycosylation sites can be produced by obligonucleotide synthesis and ligation or by site-specific mutagenesis techniques. These analog proteins can be produced in a homogenous, reduced-carbohydrate form in good yield using yeast expression systems. N-glycosylation sites in eukaryotic proteins are characterised by the amino acid triplet Asn-A_1-Z, where A_1 is any amino acid except Pro, and Z is Ser or Thr. In this sequence, asparagine profices a side chain amino group for covalent attachment of carbohydrate. Such a site can be eliminated by substituting another amino acid for Asn or for residue Z, deleting Asn or Z, or inserting a non-Z amino acid between A_1 and Z, or an amino acid other than Asn between Asn and A_1.

IL-4R derivatives may also be obtained by mutations of IL-4R or its subunits. An IL-4R mutant, as referred to herein, is a polypeptide homologous to IL-4R but which has an amino acid sequence different from native IL-4R because of a deletion, insertion or substitution. Like most mammalian genes, mammalian IL-4 receptors are presumably encoded by multi-exon genes. Alternative mRNA constructs which can be attributed to different nRNA splicing events following transcription, and which share large regions of identity or similarity with the cDNAs claimed herein, are considered to be within the scope of the present invention.

Bioequivalent analogs of IL-4R proteins may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues can be deleted or replaced with other amino acids to prevent formation of incorrect intramolecular disulfide bridges upon renaturation. Other approaches to mutagenesis involve modification of adjacent diabasic amino acid residues to enhance expression in yeast systems in which KEX2 protease activity is present. Generally, substitutions should be made conservatively; i.e., the most preferred substitute amino acids are those having physiochemical characteristics resembling those of the residue to be replaced. Similarly, when a deletion or insertion strategy is adopted, the potential effect of the deletion or insertion on biological activity should be considered.

Subunits of IL-4R may be constructed by deleting terminal or internal residues

or sequences. Particularly preferred subunits include those in which the transmembrane region and intracellular domain of IL-4R are deleted or substituted with hydrophilic residues to facilitate secretion of the receptor into the cell culture medium. The resulting protein is a soluble IL-4R molecule which may retain its ability to bind IL-4. Particular examples of soluble IL-4R include polypeptides having substantial identity to soluble murine IL-4R (1-208), soluble human IL-4R (1-207) and soluble human IL-4R (1-198), all of which retain the biological activity of soluble human IL-4R (1-207). Chimeric polypeptides comprising fragments of human and murine IL-4R may also be constructed, for example, IL-4R (1-197) Pro Ser Asn Glu Asn Leu (SEQ ID NO. 5), which is comprised of the sequence of amino acids 1-197 of human IL-4R followed by the N-terminal six amino acids of soluble murine IL-4R clone 18. This polypeptide has been found to retain the biological activity of soluble IL-4R (1-207).

To prepare pharmaceutical compositions including the peptide IL-4R the peptide is admixed with a pharmaceutically acceptable carrier or excipient which is preferably inert. Preparation of such pharmaceutical compositions are known in the art: see, for example, Remington's Pharmaceutical Sciences and U.S. Pharmacopeia: National Formulary, Mack Publishing Company, Easton, Pa. (1984).

The peptide may be administered in aqueous vehicles such as water, saline or buffered vehicles with or without various additives and/or diluting agents. A suspension, such as a zinc suspension, can be prepared to include the peptide. Such a suspension can be useful for subcutaneous (SQ) or intramuscular (IM) injection. By adjusting the proportion of zinc and the acidity, the absorption rate of the peptide can be manipulated.

The proportion of peptide and additive can be varied over a broad range so long as both are present in effective amounts. On a per-dose basis, the amount of the peptide can range from about 10 µg to about 1500 µg of each protein per kilogram body weight of the patients. A preferable range is from about 300 µg to about 800 µg.

Compositions may be ingested orally or injected into the body. Injections are usually intramuscular, subcutaneous, intradermal or intravenous. Alternatively, intra-articular injection or other routes could be used in appropriate circumstances. Additionally, compositions including the peptide IL-4R may be implanted into a patient or injected using a drug delivery system. See, for example, Urquhart, et al., Ann. Rev.

Pharmacol. Toxicol. 24: 199-236 (1984); Lewis, ed. "Controlled Release of Pesticides and Pharmaceuticals" (Plenum Press, New York, 1981); U.S. Pat. No. 3,773,919; and U.S. Pat. No. 3,270,960.

Preferably, the peptide is administered parenterally and preferably in a unit dosage injectable form. Examples of an injectable form include solutions, suspensions and emulsions. Typically, the peptide is injected in association with a pharmaceutical carrier such as normal saline, Ringer's solution, dextrose solution and other aqueous carriers known in the art. Appropriate non-aqueous carriers may also be used and examples include fixed oils and ethyl oleate. A preferred carrier is 5% dextrose in saline. Frequently, it is desirable to include additives in the carrier such as buffers and preservatives or other substances to enhance isotonicity and chemical stability.

Preferably, the peptide, IL-4R is formulated in purified form substantially free of aggregates and other proteins at a concentration of about 1 to 30 mg/ml. The concentration of the peptide in a unit dose is from about 60 micrograms to 200 milligrams varying with the application and the potency of the peptide. Although IL-4R may be administered by any of a number of routes, an intravenous infusion or bolus is preferred. Most preferably, an intravenous injection delivers about 1 mg to about 100 mg of the peptide per day. The dose range is about 15 µg to 1500 µg per kilogram of body weight of the recipient per day per peptide. Dosages should be varied according to side effects and blood cell counts which should be monitored frequently, preferably daily.

The agonist and antagonists are preferably administered intravenously. A preferred antagonist is an antibody specific for binding to IL-4. The antibodies can be chimeric, recombinant, polyclonal or monoclonal. Autologous antibodies, human or humanized antibodies are preferred for safety when human patients are being treated. The preferred single dosage of antibodies is 1-10 mg/kg body weight per antibody. Alternatively, the amount of the antibody administered in a single dose is about 10 to about 100 µg per milliliter of patient sera.

An effective amount for a particular patient may vary depending on factors such as the condition being treated, the overall health of the patient, the method route and dose of administration and the severity of side effects. Determination of the appropriate dose is made by the clinician using parameters known in the art. Generally, the dose

begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achi ved.

The total daily dose of the peptide can be given as bolus injection, such as an intravenous injection, or it can be given as a continuous infusion. Alternatively, the daily dosage may be divided into several smaller doses for multiple bolus intravenous administration. Other routes of administration such as intramuscular injection, can be employed.

In one aspect of the invention, there is provided a method which comprises co-administering to the mammal an effective amount of each of agonist or antagonist to IL-4 and one or more anti-viral agents. The mammal is preferably a human. The co-administering can be simultaneous or sequential. Generally, "co-administering" means that the cytokine is present in the recipient during a specified time interval. Typically, the anti-viral agent is administered within the half life of the cytokine. Preferably, the co-administration is parenteral, and most preferably it is intravenous. The effective amount is selected from a range from about 15 µg to about 1500 µg per kilogram of body weight of the mammal.

Mutations in nucleotide sequences constructed for expression of analog IL-4Rs must, of course, preserve the reading frame phase of the coding sequences and preferably will not create complementary regions that could hybridise to produce secondary mRNA structures, such as loops or hairpins, which would adversely affect translation of the receptor mRNA. Although a mutation site may be predetermined, it is not necessary that the nature of the mutation per se be predetermined. For example, in order to select for optimum characteristics of mutants at a given site, random mutagenesis may be conducted at the target codon and the expressed IL-4R mutants screened for the desired activity.

This invention includes (among others) treatments against viral, bacterial, and mycoplasma infections by any suitable route including enteric, parenteral, topical, oral, rectal, nasal or vaginal routes. Parenteral routes include subcutaneous, intramuscular, intravenous and sublingual administration. The preferred route of administration would be an intravenous one but this may not be feasible with a large patient base and oral administration of compounds may be the most preferred route.

The Antagonists are preferably administered intravenously. A preferred

antagonist is an antibody specific for binding to IL-4. The antibodies can be chimeric, recombinant, polyclonal or monoclonal. Autologous antibodies, human or humanized antibodies are preferred for safety when human patients are being treated. The preferred single dosage of antibodies is 1-10 mg/kg body weight per antibody. Alternatively, the amount of the antibody administered in a single dose is about 10 to about 100 µg per milliliter of patient sera.

Patient Treatment

The patient was HIV+ and had been taking a combination course of both reverse transcriptase inhibitors combined with Protease inhibitors. His viral load had decreased initially upon the commencement of the Protease and Reverse transcriptase inhibitors combination therapy regime. However, his CD4 absolute and percentage values did not show any improvement with this conventional therapy. See Figs. 3A, 3B, 3C and 3D wherein the patient was monitored over a period of 208 days during which he was receiving various therapies as per the present invention. Treatment A, herein the patient stopped all his standard therapy and was administered Anti-serum to IL-10 (Recombinant Human). During this period viral reproduction was observed. Over a period of 14 days, the HIV-I RNA g PCR rose from 15,384 to 157,812. The bloodwork analysis obtained by the administration of a Th_2 cytokine antibody alone (no anti viral treatment) is contrary to the teaching of International Publication Number WO 94/06473. The patient was maintained on his original conventional (Protease and Reverse transcriptase inhibitors) therapy but he was also co-administered rabbit generated polyclonal Antiserum to human Interleukin 10 and human Interleukin 4, treatment B Figs. 3A, 3B, 3C and 3D. The antibody class was IgG and the respective antigens were recombinant human IL-10 and recombinant human IL-4 (see Tables A and B, below).

TABLE A

DESCRIPTION:	Anti-serum to recombinant human IL-l0
FORM:	Liquid
RECOMMENDED DILUENT:	Tris Buffered Saline
CONCENTRATION:	0.65 mg/ml
STABILIZERS:	none
PRESERVATIVE:	none
STERILITY:	Sterile filtered (0.2um)
HOST SPECIES:	Rabbit
ANTIBODY CLASS:	IgG
ANTIGEN USED:	Recombinant human IL-l0
METHOD OF PURIFICATION:	Ion exchange chromatography
METHOD OF QUANTITATION:	Pierce BCA Protein Assay
SPECIFICITY:	Human IL-10
CROSS-REACTIVITY:	No cross reactivity with WHO standards: IL-1-alpha, IL-1-beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-11, IL-15, EGF, FGFa, FGFb, GM-CSF, GRO-alpha, IGF-1, IGF-11, IFN-alpha, IFN-gamma, MIP-1-alpha, MIP-1-beta, MCAF, MCP-2, MCP-3,PDGF-aa, RANTES, TGF-alpha, TNF-alpha, TNF-beta, TPO, VEGF, murine IL-1-alpha, murine IL-1-beta, and IgG done by EIA.
SPECIES TESTED:	Human by EIA
MINIMUM DILUTION:	1:100
STORAGE:	Short term 4°C and -20°C for long term

TABLE B

DESCRIPTION:	Anti-serum to recombinant human IL-4
SPECIFICITY:	Human IL-4
PRODUCT FORM:	Liquid
RECOMMENDED DILUENT:	Tris Buffered Saline
STABILIZERS:	none
PRESERVATIVES:	none
ANTIBODY CLASS:	IgG
CONCENTRATION:	2.14mg/ml
ANTIGEN USED TO GENERATE:	Recombinant human IL-4
PURIFICATION:	
Method of purification:	Ion exchange chromatography
Method of quantitation:	Pierce BCA Protein Assay
CROSS-REACTIVITY:	No cross reactivity with WHO standards: IL-1-alpha, IL-1-beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-11, IL-13, IL-15, EGF, FGFa, FGFb, GM-CSF, GRO-alpha, IGF-1, IGF-11, IFN-alpha, IFN-garnma, MIP-1-alpha, MIP-1-beta, MCAF, MCP-2, MCP-3, PDGF-aa, RANTES, TGF-alpha, TNF-alpha, TNF-beta, TPO, VEGF, murine IL-1-alpha, murine IL-1-beta, and IgG done by EIA
MINIMUM DILUTION:	1:100
STORAGE:	Short term 2-8°C long term at -20°C

The dosage used was 2 mg/ml of each antibody and 2 mls was administered IV every day for seven days. The results were that viral load as measured by PCR decreased by one log the first week of the injections and to undetectable levels by the following week (14 days < 400 copies). The Helper T (CD4) absolute and percentage readings changed from 177 (wk. 0) to 276 (wk. 1) and from 11% (wk.0) to 15% (wk. I). There was a simultaneous decrease in suppresser T(CD8) percentage from 73% (wk.0) to 67% (wk.1). The patient experienced some flu-like symptoms immediately following the injections but no toxicity or discomfort were reported for this therapy. The patient showed a rapid development of anti-rabbit antibodies and further therapy required the

use of monoclonal Antibodies utilize the human receptor (recombinant) to either one or both of Interleukin-4 or Interleukin-10. This cytokine removal therapy has demonstrated a dramatic ability to augment conventional combination anti-viral therapy and to rapidly lower viral load levels so that fewer viruses have long term exposure to the anti-viral drugs to allow resistant strain development. Also from our analysis of HIV viral strain removal it would appear from the viral isolates present before and after this cytokine antibody therapy that Protease and R. T. resistant strains were cleared by the patient's immune system similar to naïve strains. Treatment C relates to a period when the patient maintained his conventional therapy and was administered only anti-serum to IL-10. From other HIV patient studies which utilzed the similar administration of the antibodies to recombinant human Interleukin 4 and/or Interleukin 10 it was demonstrated that whilst the co-administration of conventional anti-viral drugs that the removal of these cytokines (IL-4/IL-10) without the presence of concurrent anti-viral drugs to suppress viral replication that a 3 log increase in PCR viral levels occurred within 2 weeks of antibody therapy.

CLAIMS

1. A method of enhancing immune response in a patient, said method comprising a combination therapy containing one or mor anti-viral agent and one or more agonist and/or Antagonist to a Th_2 cytokine.

2. A method of treating a viral infection in a mammal, human or animal, said method comprising a combination therapy containing one or more anti-viral agent and one or more agonist and/or Antagonist to a Th_2 cytokine.

3. A method of treating a condition in a mammal, human or animal, said method comprising a combination therapy containing one or more anti-viral agent and one or more agonist and/or Antagonist to a Th_2 cytokine.

4. A pharmaceutical formulation containing one or more anti-viral agent and one or more agonist and/or Antagonist to a Th_2 cytokine.

5. A method of administration to a patient a pharmaceutical formulation containing one or more anti-viral agent and one or more agonist and/or antagonist to a Th_2 cytokine.

6. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising a combination therapy containing one or more anti-viral agent and Agonist and/or Antagonist to a Th_2 cytokine.

7. A combination therapy comprising the administration to a patient one or more anti-viral agents and one or more agonist and/or Antagonist to a Th_2 cytokine.

8. A method of enhancing immune response in a patient, said method comprising a combination therapy containing a protease inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

9. A method of treating a viral infection in a mammal, human or animal, said method comprising a combination therapy containing a protease inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

10. A method of treating a condition in a mammal, human or animal, said method comprising a combination therapy containing a protease inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

11. A pharmaceutical formulation containing a protease inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

12. A method of administration to a patient a pharmaceutical formulation containing a protease inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

13. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising a combination therapy containing a protease inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

14. A combination therapy comprising the administration to a patient a protease inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

15. A method of enhancing immune response in a patient, said method comprising a combination therapy containing a reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

16. A method of treating a viral infection in a mammal, human or animal, said method comprising a combination therapy containing a reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

17. A method of treating a condition in a mammal, human or animal, said method comprising a combination therapy containing a reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

18. A pharmaceutical formulation containing a reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

19. A method of administration to a patient a pharmaceutical formulation containing a reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

20. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising a combination therapy containing reverse transcriptase inhibitor and one or more agonist and/or antagonist to a Th_2 cytokine.

21. A combination therapy comprising the administration to a patient a protease inhibitor and a receptor to Interleukin-4.

22. A method of enhancing immune response in a patient, said method comprising administering an amount of a receptor to Interleukin-4 in combination with one or more protease inhibitors.

23. A method of treating a viral infection in a mammal, human or animal, said method comprising administering an amount of receptor to Interleukin-4 in combination

with one or more protease inhibitors.

24. A method of treating a condition in a mammal, human or animal, said method comprising administering an amount of receptor to Interleukin-4 in combination with one or more protease inhibitors.

25. A pharmaceutical formulation containing a receptor to Interleukin-4 in combination with one or more protease inhibitors.

26. A method of administration to a patient a pharmaceutical formulation containing a receptor to Interleukin-4 in combination with one or more protease inhibitors.

27. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising administering to said mammal a receptor to Interleukin-4 in combination with one or more protease inhibitors.

28. A combination therapy according to any one of claims 1, 2, 3, 6 - 10, 13 - 17, 21, 22, 43 - 45, and 48 - 51, wherein each component of the combination is administered jointly or at different stages of a treatment regimen.

29. A Th_2 cytokine according to any one of claims 1 - 21 and 43 - 50, wherein the cytokine is one or more of the following: Interleukin-3, Interleukin-4, Interleukin-5, Interleukin-6, Interleukin-9, Interleukin-10, Interleukin-13 and Cytokine GM-CSF.

30. A method according to any one of claims 1, 3, 5, 10 - 12, 15, 16, 19 - 21, 24, 25, 27, 45, 46, 47, 50, 53, 54 and 56, wherein the mammal or patient has a neoplastic condition.

31. A protease inhibitor according to claim 8,9,10,11,12, l3,14,21,22,23,24,25,26 & 27 wherein the Protease Inhibitor may be one or more of the following Inviase (saquinavir, RO-31-8959) Hoffmann-La Roche. Norvir (ritonavir, ABT-538, Abbott. Crixivan (indinavir, MK-639), Agouron Viracept (nelfrnavir, AG-1343) Agouron. VX-478 141w94 Glaxo-Wellcome/Vertex, KNI-272 (kynostatin), Nikko Kyoto, Pharmaceutical and National Cancer Institute. U-103373, Upjohn. CGP-53437, Ciba-Geigy. Hoe/Bay-793, Hoechst-Bayer. SR-41476, Sanofi.

32. A reverse transcriptase inhibitor according to claims15-20 inclusive wherein the inhibitor may be one or more of the following AZT (Retrovir, zidovudine), ddI(Videx, didanosine), ddC (Hivid, zalcitabine), d4T (Zerit, stavudine), 3TC (Epivir, Lamivudine).

33. Agonist and/or antagonist according to any one of claims 1 - 21 and 43 - 50, wherein the agonist and/or antagonist is an antibody specific to a Th_2 cytokine, wherein the antibodies are chimeric, recombinant, polyclonal, monoclonal or antibodies of plant origin.

34. Agonist and/or antagonist according to any one of claims 1 - 21 and 43 - 50, wherein the agonist and/or antagonist is a receptor or mutein receptor to specific Th_2 cytokines.

35. A method of enhancing viral replication in a patient, said method comprising a pharmaceutical formulation containing an agonist and/or antagonist to a Th_2 cytokine.

36. A method according to claim 35, wherein the cytokine is at least one member of the group consisting of IL-4, IL-5, IL-6, IL-10 and IL-13.

37. A method according to claim 35 or 36, wherein the Th_2 cytokine is selected from the group consisting of IL-4, IL-5, IL-6, IL-10 and IL-13.

38. A method according to any one of claims 22 - 27 and 51 - 56, wherein the receptor to the cytokines is administered by IV, enema or transdermal patch in dose amounts of between 10 and 1000 micrograms per day.

39. A method according to any one of claims 22 - 27 and 51 - 56, wherein the receptor to the cytokines is administered as a soluble receptor.

40. A combination therapy according to any one of claims 1 - 3, 6, 8, 9, 10, 13 - 17, 20, 21, 28, 43 - 45, and 48 - 50, wherein the combination therapy is sequentially co-administered.

41. A combination therapy according to any one of claims 1 - 3, 6, 8, 9, 10, 13 - 17, 20, 21, 28, 43 - 45 and 48 - 50, wherein the combination therapy is parenterally co-administered.

42. A combination therapy according to any one of claims 1-3,6,8,9,10, 13-17,20,21,28,43-45 and 48-50, wherein the combination therapy is intravenously co-administered.

43. A method of enhancing immune response in a patient, said method comprising a combination therapy containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th_2 cytokine.

44. A method of treating a viral infection in a mammal, human or animal, said method comprising a combination therapy containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th_2 cytokine.

45. A method of treating a condition in a mammal, human or animal, said method comprising a combination therapy containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th_2 cytokine.

46. A pharmaceutical formulation containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th_2 cytokine.

47. A method of administration to a patient a pharmaceutical formulation containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th_2 cytokine.

48. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising a combination therapy containing a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th_2 cytokine.

49. A combination therapy comprising the administration to a patient a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and one or more agonist and/or antagonist to a Th_2 cytokine.

50. A combination therapy comprising the administration to a patient of a compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor, and a receptor to Interleukin-4.

51. A method of enhancing immune response in a patient, said method comprising administering an amount of a receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

52. A method of treating a viral infection in a mammal, human or animal, said method comprising administering an amount of receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

53. A method of treating a condition in a mammal, human or animal, said method comprising administering an amount of receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

54. A pharmaceutical formulation containing a receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

55. A method of administration to a patient a pharmaceutical formulation containing a receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

56. A method of providing an immunosuppressive or immunoregulatory effect in a mammal, human or animal, comprising administering to said mammal a receptor to Interleukin-4 in combination with one or more compound of Formula 1 or a metabolite, analog or precursor of any such compound, or a pharmaceutically acceptable salt of any such compound, metabolite, analog or precursor.

57. A method of enhancing immune response in a patient in need of such enhancement, comprising administering to said patient (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th_2 cytokine.

58. A method of treating viral infection, bacterial infection, fungal infection, parasitic infection and/or infectious protein units in a patient in need of such treatment, or minimizing the likelihood of such infection and/or reducing the potential future adversity of such infection in a patient, comprising administering to said patient (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th_2 cytokine.

59. A method of providing immunosuppression or immunoregulatory effect in patient in need such effect, comprising administering to said patient (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th_2 cytokine.

60. A method as recited in any one of claims 57-59, wherein said patient is a mammal.

61. A method as recited in any one of claims 57-60, wherein said viral infection is a retroviral infection.

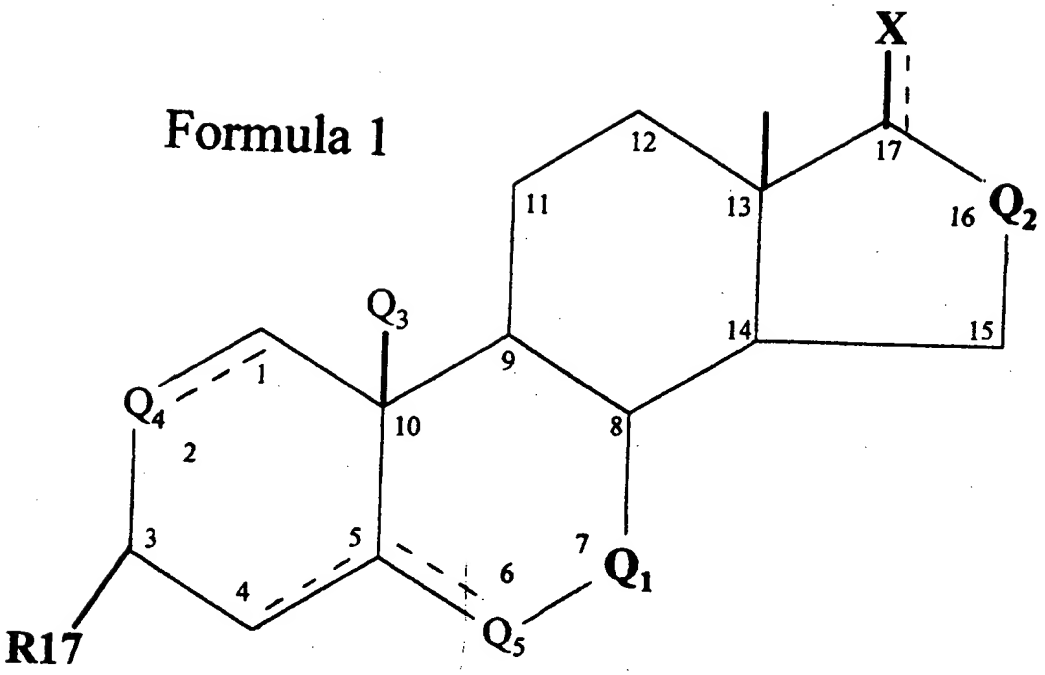
62. A method as recited in claim 61, wherein said viral infection is HIV.

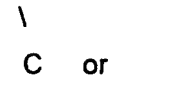
63. A method as recited in any one of claims 57-62, wherein said anti-viral agent comprises at least one protease inhibitor.

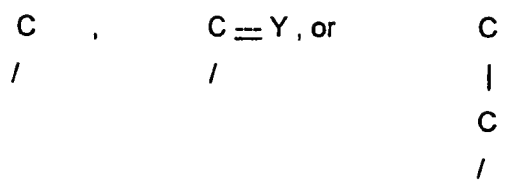
64. A method as recited in any one of claims 57-63, wherein said anti-viral agent comprises at least one reverse transcriptase inhibitor.

65. A method as recited in any one of claims 57-64, wherein said anti-viral agent comprises at least one compound selected from the group consisting of:

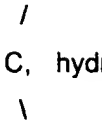
Formula 1

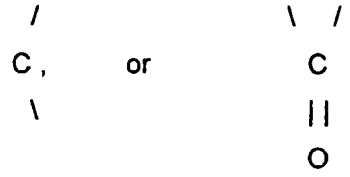


wherein Q_1 is  ,

wherein Q_2 is  ,

wherein Q_3 is H or CH_3

wherein Q_4 is  hydroxyvinylidene, oxy or methyl methylene;

wherein Q_5 is  ,

wherein no hydrogen atoms, some hydrogen atoms or all hydrogen atoms are independently replaced by halogen (such as Br, Cl, F or I), hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkyl or -S-CN,

wherein the broken lines between the 1- and 2-positions, the 4- and 5-positions and the 5- and 6- positions, as well as the broken line adjacent the 17 position and the broken line in the definition of Q_2, each independently represents a single bond or a double bond,

or a metabolite, analog, or precursor of any such compound, or a salt of any such compound, metabolite, analog or precursor.

66. A method as recited in any one of claims 57-65, wherein said at l ast one agonist and/or at least one antagonist to a Th_2 cytokine comprises IL-4 receptor.

67. A method as recited in any one of claims 57-65, wherein said at least one agonist and/or at least one antagonist to a Th_2 cytokine comprises at least one agonist or antagonist to a Th_2 cytokine selected from the group consisting of IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13 and GM-CSF.

68. Use of (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th_2 cytokine in the manufacture of a medicament for enhancing immune response in a patient in need of such enhancement.

69. Use of (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th_2 cytokine in the manufacture of a medicament for treating viral infection, bacterial infection, fungal infection, parasitic infection and/or infectious protein units in a patient in need of such treatment, or for minimizing the likelihood of such infection and/or reducing the potential future adversity of such infection in a patient.

70. Use of (1) at least one anti-viral agent and (2) at least one agonist and/or at least one antagonist to a Th_2 cytokine in the manufacture of a medicament for providing immunosuppression or immunoregulatory effect in patient in need such effect.

71. A use as recited in any one of claims 68-70, wherein said patient is a mammal.

72. A use as recited in any one of claims 68-71, wherein said viral infection is a retroviral infection.

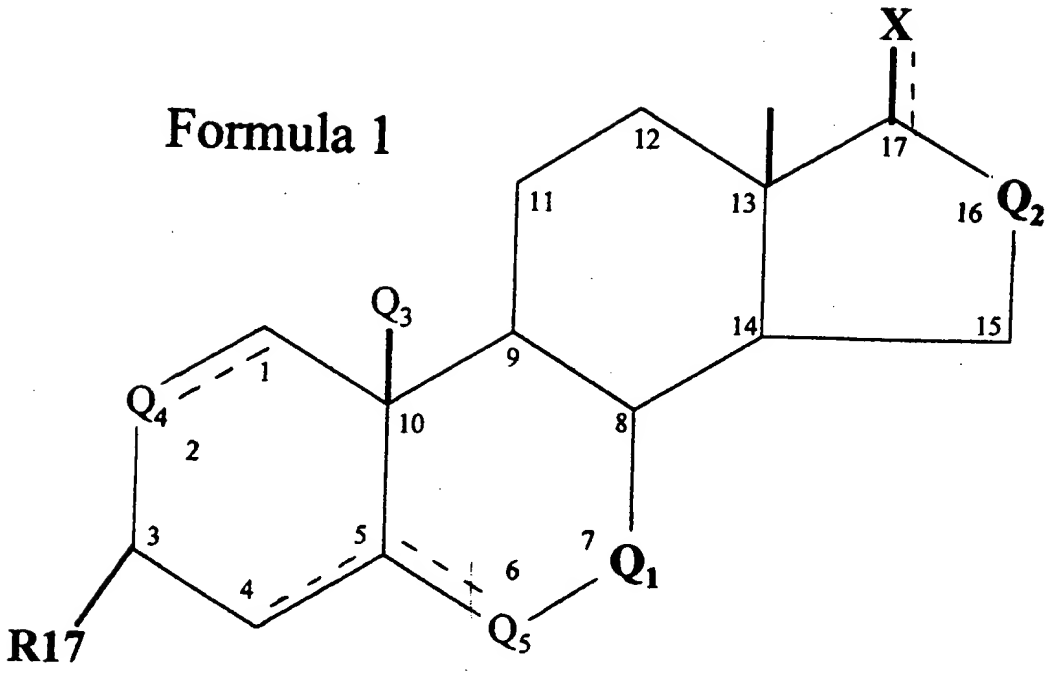
73. A use as recited in claim 72, wherein said viral infection is HIV.

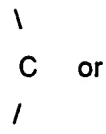
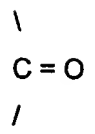
74. A use as recited in any one of claims 68-73, wherein said anti-viral agent comprises at least one protease inhibitor.

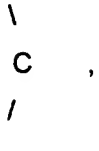
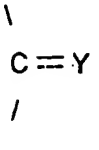
75. A use as recited in any one of claims 68-74, wherein said anti-viral agent comprises at least one reverse transcriptase inhibitor.

76. A use as recited in any one of claims 68-75, wherein said anti-viral agent comprises at least one compound selected from the group consisting of:

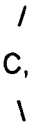
Formula 1

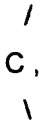
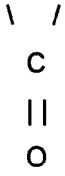


wherein Q_1 is  or  ,

wherein Q_2 is  ,  , or 

wherein Q_3 is H or CH_3

wherein Q_4 is  hydroxyvinylidene, oxy or methyl methylene;

wherein Q_5 is  , or 

wherein no hydrogen atoms, some hydrogen atoms or all hydrogen atoms are independently replaced by halogen (such as Br, Cl, F or I), hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkyl or -S-CN,

wherein the broken lines between the 1- and 2-positions, the 4- and 5-positions and the 5- and 6- positions, as well as the broken line adjacent the 17 position and the broken line in the definition of Q_2, each independently represents a single bond or a double bond,

or a metabolite, analog, or precursor of any such compound, or a salt of any such compound, metabolite, analog or precursor.

77. A use as recited in any one of claims 68-76, wherein said at least one agonist and/or at least one antagonist to a Th_2 cytokine comprises IL-4 receptor.

78. A use as recited in any one of claims 68-76, wherein said at least one agonist and/or at least one antagonist to a Th_2 cytokine comprises at least one agonist or antagonist to a Th_2 cytokine selected from the group consisting of IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13 and GM-CSF.

79. A method of reducing proviral DNA in a patient in need of such reduction, comprising administering to said patient (1) at least one anti-viral agent, and (2) at least one agonist and/or at least one antagonist to a Th_2 cytokine.

80. A method as recited in claim 79, further comprising administering to said patient at least one Th_2 cytokine.

81. A method as recited in claim 79, further comprising administering to said patient said Th_2 cytokine.

82. A method as recited in claim 81, wherein said Th_2 cytokine is IL-4.

83. A method of enhancing immune response in a patient in need of such enhancement, comprising administering to said patient (1) at least one Th_2 cytokine and (2) at least one agonist and/or at least one antagonist to said Th_2 cytokine.

84. A method of treating viral infection, bacterial infection, fungal infection, parasitic infection and/or infectious protein units in a patient in need of such treatment, or minimizing the likelihood of such infection and/or reducing the potential future adversity of such infection in a patient, comprising administering to said patient (1) at least one Th_2 cytokine and (2) at least one agonist and/or at least one antagonist to said Th_2 cytokine.

85. A method of providing immunosuppression or immunoregulatory effect in patient in need such effect, comprising administering to said patient (1) at least one Th_2 cytokine and (2) at least one agonist and/or at least one antagonist to said Th_2 cytokine.

86. A method as recited in any one of claims 83-85, wherein said Th_2 cytokine is IL-4.

87. A composition comprising:

(1) at least one anti-viral agent, and

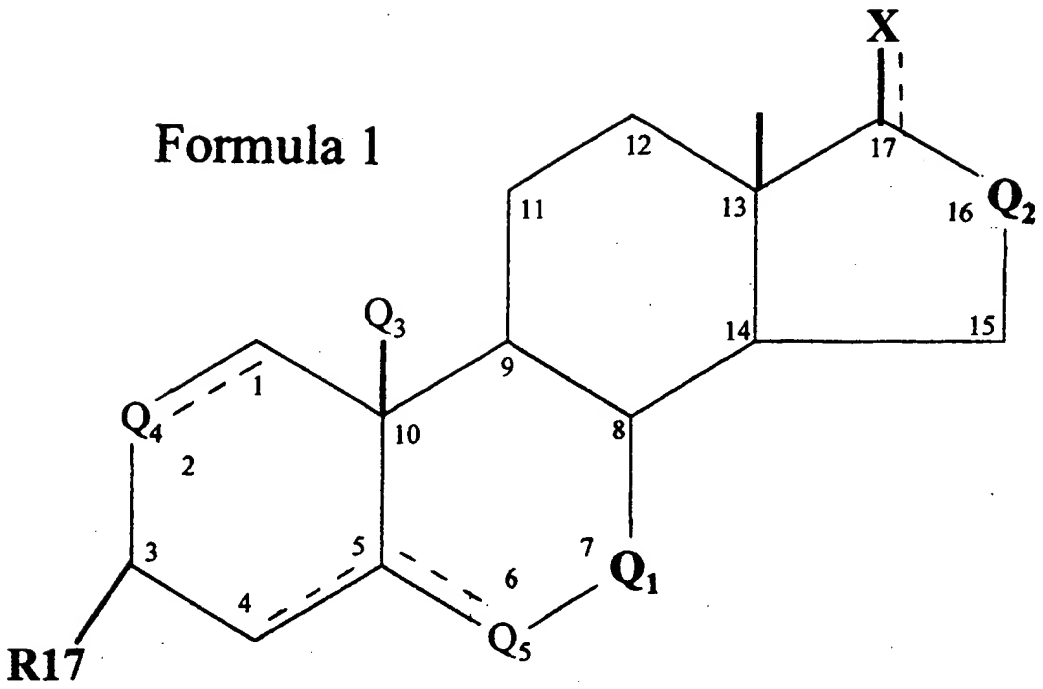
(2) at least one agonist and/or at least one antagonist to a Th_2 cytokine.

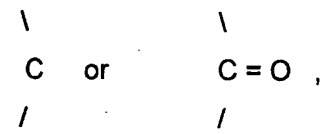
88. A composition as recited in claim 87, wherein said anti-viral agent comprises at least one protease inhibitor.

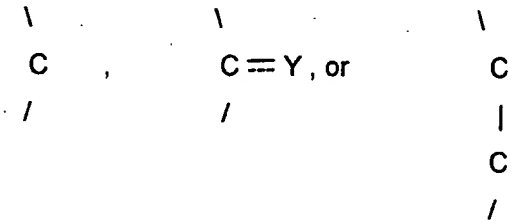
89. A composition as recited in claim or claim 88, wherein said anti-viral agent comprises at least one reverse transcriptase inhibitor.

90. A composition as recited in any one of claims 87-89, wherein said anti-viral agent comprises at least one compound selected from the group consisting of

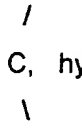
Formula 1

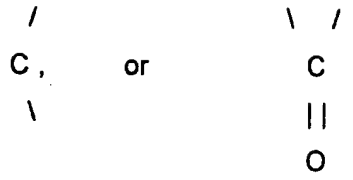


wherein Q_1 is  ,

wherein Q_2 is  ,

wherein Q_3 is H or CH_3

wherein Q_4 is  C, hydroxyvinylidene, oxy or methyl m thylene;

wherein Q_5 is  or

wherein no hydrogen atoms, some hydrogen atoms or all hydrogen atoms are independently replaced by halogen (such as Br, Cl, F or I), hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkyl or -S-CN,

wherein the broken lines between the 1- and 2-positions, the 4- and 5-positions and the 5- and 6- positions, as well as the broken line adjacent the 17 position and the broken line in the definition of Q_2, each independently represents a single bond or a double bond,

or a metabolite, analog, or precursor of any such compound, or a salt of any such compound, metabolite, analog or precursor.

91. A composition as recited in any one of claims 87-90, wherein said at least one agonist and/or at least one antagonist to a Th_2 cytokine comprises IL-4 receptor.

92. A composition as recited in any one of claims 87-90, wherein said at least one agonist and/or at least one antagonist to a Th_2 cytokine comprises at least one agonist or antagonist to a Th_2 cytokine selected from the group consisting of IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13 and GM-CSF.

93. A kit comprising:

(1) unit dosages of at least one anti-viral agent, and

(2) unit dosages of at least one agonist and/or at least one antagonist to a Th_2 cytokine.

FIGURE 1A

```
ATG GGG CGG CTT TGC ACC AAG TTC CTG ACC TCT GTG GGC TGT CTG -31
Met Gly Arg Leu Cys Thr Lys Phe Leu Thr Ser Val Gly Cys Leu -11

ATT TTG CTG TTG GTG ACT GGA TCT GGG AGC ATC AAG GTC CTG GGT 15
Ile Leu Leu Leu Val Thr Gly Ser Gly Ser Ile Lys Val Leu Gly 5

GAG CCC ACC TGC TTC TCT GAC TAC ATC CGC ACT TCC ACG TGT GAG 60
Glu Pro Thr Cys Phe Ser Asp Tyr Ile Arg Thr Ser Thr Cys Glu 20

TGG TTC CTG GAT AGC GCT GTG GAC TGC AGT TCT CAG CTC TGC CTA 105
Trp Phe Leu Asp Ser Ala Val Asp Cys Ser Ser Gln Leu Cys Leu 35

CAC TAC AGG CTG ATG TTC TTC GAG TTC TCT GAA AAC CTC ACA TGC 150
His Tyr Arg Leu Met Phe Phe Glu Phe Ser Glu Asn Leu Thr Cys 50

ATC CCG AGG AAC AGT GCC AGC ACT GTG TGT GTG TGC CAC ATG GAA 195
Ile Pro Arg Asn Ser Ala Ser Thr Val Cys Val Cys His Met Glu 65

ATG AAT AGG CCG GTC CAA TCA GAC AGA TAC CAG ATG GAA CTG TGG 240
Met Asn Arg Pro Val Gln Ser Asp Arg Tyr Gln Met Glu Leu Trp  80

GCT GAG CAC AGA CAG CTG TGG CAG GGC TCC TTC AGC CCC AGT GGT 285
Ala Glu His Arg Gln Leu Trp Gln Gly Ser Phe Ser Pro Ser Gly 95

AAT GTG AAG CCC CTA GCT CCA GAC AAC CTC ACA CTC CAC ACC AAT 330
Asn Val Lys Pro Leu Ala Pro Asp Asn Leu Thr Leu His Thr Asn 110

GTG TCC GAC GAA TGG CTG CTG ACC TGG AAT AAC CTG TAC CCA TCG 375
Val Ser Asp Glu Trp Leu Leu Thr Trp Asn Asn Leu Tyr Pro Ser 125

AAC AAC TTA CTG TAC AAA GAC CTC ATC TCC ATG GTC AAC ATC TCC 420
Asn Asn Leu Leu Tyr Lys Asp Leu Ile Ser Met Val Asn Ile Ser 140

AGA GAG GAC AAC CCT GCA GAA TTC ATA GTC TAT AAT GTG ACC TAC 465
Arg Glu Asp Asn Pro Ala Glu Phe Ile Val Tyr Asn Val Thr Tyr 155

AAG GAA CCC AGG CTG AGC TTC CCG ATC AAC ATC CTG ATG TCA GGG 510
Lys Glu Pro Arg Leu Ser Phe Pro Ile Asn Ile Leu Met Ser Gly 170

GTC TAC TAT ACG GCG CGT GTG AGG GTC AGA TCC CAG ATA CTC ACT 555
Val Tyr Tyr Thr Ala Arg Val Arg Val Arg Ser Gln Ile Leu Thr 185

GGC ACC TGG AGT GAG TGG AGT CCT AGC ATC ACG TGG TAC AAC CAC 600
Gly Thr Trp Ser Glu Trp Ser Pro Ser Ile Thr Trp Tyr Asn His 200

TTC CAG CTG CCC CTG ATA CAG CGC CTT CCA CTG GGG GTC ACC ATC 645
Phe Gln Leu Pro Leu Ile Gln Arg Leu Pro Leu Gly Val Thr Ile 215

TCC TGC CTC TGC ATC CCG TTG TTT TGC CTG TTC TGT TAC TTC AGC 690
Ser Cys Leu Cys Ile Pro Leu Phe Cys Leu Phe Cys Tyr Phe Ser 230

ATT ACC AAG ATT AAG AAG ATA TGG TGG GAC CAG ATT CCC ACC CCA 735
Ile Thr Lys Ile Lys Lys Ile Trp Trp Asp Gln Ile Pro Thr Pro 245
```

FIGURE 1B

```
GCA CGC AGT CCC TTG GTG GCC ATC ATC ATT CAG GAT GCA CAG GTG 780
Ala Arg Ser Pro Leu Val Ala Ile Ile Ile Gln Asp Ala Gln Val 260

CCC CTC TGG GAT AAG CAG ACC CGA AGC CAG GAG TCA ACC AAG TAC 825
Pro Leu Trp Asp Lys Gln Thr Arg Ser Gln Glu Ser Thr Lys Tyr 275

CCG CAC TGG AAA ACT TGT CTA GAC AAG CTG CTG CCT TGC TTG CTG 870
Pro His Trp Lys Thr Cys Leu Asp Lys Leu Leu Pro Cys Leu Leu 290

AAG CAC AGA GTA AAG AAG AAG ACA GAC TTC CCG AAG GCT GCC CCA 915
Lys His Arg Val Lys Lys Lys Thr Asp Phe Pro Lys Ala Ala Pro 305

ACC AAG TCT CTC CAG AGT CCT GGA AAG GCA GGC TGG TGT CCC ATG 960
Thr Lys Ser Leu Gln Ser Pro Gly Lys Ala Gly Trp Cys Pro Met 320

GAG GTC AGC AGG ACC GTC CTC TGG CCA GAG AAT GTT AGT GTC AGT 1005
Glu Val Ser Arg Thr Val Leu Trp Pro Glu Asn Val Ser Val Ser 335

GTG GTG CGC TGT ATG GAG CTG TTT GAG GCC CCA GTA CAG AAT GTG 350
Val Val Arg Cys Met Glu Leu Phe Glu Ala Pro Val Gln Asn Val 350

GAG GAG GAA GAA GAT GAG ATA GTC AAA GAG GAC CTG AGC ATG TCA 1095
Glu Glu Glu Glu Asp Glu Ile Val Lys Glu Asp Leu Ser Met Ser 365

CCT GAG AAC AGC GGA GGC TGC GGC TTC CAG GAG AGC CAG GCA GAC 1140
Pro Glu Asn Ser Gly Gly Cys Gly Phe Gln Glu Ser Gln Ala Asp 380

ATC ATG GCT CGG CTC ACT GAG AAC CTG TTT TCC GAC TTG TTG GAG 1185
Ile Met Ala Arg Leu Thr Glu Asn Leu Phe Ser Asp Leu Leu Glu 395

GCT GAG AAT GGG GGC CTT GGC CAG TCA GCC TTG GCA GAG TCA TGC 1230
Ala Glu Asn Gly Gly Leu Gly Gln Ser Ala Leu Ala Glu Ser Cys 410

TCC CCT CTG CCT TCA GGA AGT GGG CAG GCT TCT GTA TCC TGG GCC 1275
Ser Pro Leu Pro Ser Gly Ser Gly Gln Ala Ser Val Ser Trp Ala 425

TGC CTC CCC ATG GGG CCC AGT GAG GAG GCC ACA TGC CAG GTC ACA 1320
Cys Leu Pro Met Gly Pro Ser Glu Glu Ala Thr Cys Gln Val Thr 440

GAG CAG CCT TCA CAC CCA GGC CCT CTT TCA GGC AGC CCA GCC CAG 1365
Glu Gln Pro Ser His Pro Gly Pro Leu Ser Gly Ser Pro Ala Gln  455

AGT GCA CCT ACT CTG GCT TGC ACG CAG GTC CCA CTT GTC CTT GCA 1410
Ser Ala Pro Thr Leu Ala Cys Thr Gln Val Pro Leu Val Leu Ala 470

GAC AAT CCT GCC TAC CGG AGT TTT AGT GAC TGC TGT AGC CCG GCC 1455
Asp Asn Pro Ala Tyr Arg Ser Phe Ser Asp Cys Cys Ser Pro Ala 485

CCA AAT CCT GGA GAG CTG GCT CCA GAG CAG CAG CAG GCT GAT CAT 1500
Pro Asn Pro Gly Glu Leu Ala Pro Glu Gln Gln Gln Ala Asp His 500

CTG GAA GAA GAG GAG CCT CCA AGC CCG GCT GAC CCC CAT TCT TCA 1545
Leu Glu Glu Glu Glu Pro Pro Ser Pro Ala Asp Pro His Ser Ser 515
```

FIGURE 1C

```
GGG CCA CCA ATG CAG CCA GTG GAG AGC TGG GAG CAG ATC CTT CAC 1590
Gly Pro Pro Met Gln Pro Val Glu Ser Trp Glu Gln Ile Leu His 530

ATG AGT GTC CTG CAG CAT GGG GCA GCT GCT GGC TCC ACC CCA GCC 1635
Met Ser Val Leu Gln His Gly Ala Ala Ala Gly Ser Thr Pro Ala 545

CCT GCC GGT GGC TAC CAG GAG TTT GTG CAG GCA GTG AAG CAG GGT 1680
Pro Ala Gly Gly Tyr Gln Glu Phe Val Gln Ala Val Lys Gln Gly 560

GCC GCC CAG GAT CCT GGG GTG CCT GGT GTC AGG CCT TCT GGA GAC 1725
Ala Ala Gln Asp Pro Gly Val Pro Gly Val Arg Pro Ser Gly Asp 575

CCC GGT TAC AAG GCC TTC TCG AGC CTG CTC AGC AGC AAT GGC ATC 1770
Pro Gly Tyr Lys Ala Phe Ser Ser Leu Leu Ser Ser Asn Gly Ile 590

CGC GGG GAC ACA GCA GCA GCG GGG ACT GAC GAT GGG CAT GGA GGC 1815
Arg Gly Asp Thr Ala Ala Ala Gly Thr Asp Asp Gly His Gly Gly 605

TAC AAG CCC TTC CAG AAT CCT GTT CCT AAC CAG TCC CCT AGC TCC 1862
Tyr Lys Pro Phe Gln Asn Pro Val Pro Asn Gln Ser Pro Ser Ser 620

GTG CCC TTA TTT ACT TTC GGA CTA GAC ACG GAG CTG TCA CCC AGT 1905
Val Pro Leu Phe Thr Phe Gly Leu Asp Thr Glu Leu Ser Pro Ser 635

CCT CTG AAC TCA GAC CCA CCC AAA AGC CCC CCA GAA TGC CTT GGT 1950
Pro Leu Asn Ser Asp Pro Pro Lys Ser Pro Pro Glu Cys Leu Gly 650

CTG GAG CTG GGG CTC AAA GGA GGT GAC TGG GTG AAG GCC CCT CCT 1995
Leu Glu Leu Gly Leu Lys Gly Gly Asp Trp Val Lys Ala Pro Pro 665

CCT GCA GAT GAG GTG CCC AAG CCC TTT GGG GAT GAC CTG GGC TTT 2040
Pro Ala Asp Glu Val Pro Lys Pro Phe Gly Asp Asp Leu Gly Phe 680

GGT ATT GTG TAC TCG TCC CTC ACT TGC CAC TTG TGT GGC CAC CTG 2085
Gly Ile Val Tyr Ser Ser Leu Thr Cys His Leu Cys Gly His Leu 695

AAG CAA CAC CAC AGC CAG GAG GAA GGT GGC CAG AGC CCC ATC GTT 2130
Lys Gln His His Ser Gln Glu Glu Gly Gly Gln Ser Pro Ile Val 710

GCT AGC CCT GGC TGT GGC TGC TGC TAC GAT GAC AGA TCA CCA TCC 2175
Ala Ser Pro Gly Cys Gly Cys Cys Tyr Asp Asp Arg Ser Pro Ser 725

CTG GGG AGC CTC TCG GGG GCC TTG GAA AGC TGT CCT GAG GGA ATA 2220
Leu Gly Ser Leu Ser Gly Ala Leu Glu Ser Cys Pro Glu Gly Ile 740

CCA CCA GAA GCC AAC CTC ATG TCA GCA CCC AAG ACA CCC TCA AAC 2265
Pro Pro Glu Ala Asn Leu Met Ser Ala Pro Lys Thr Pro Ser Asn 755

TTG TCA GGG GAG GGC AAG GGC CCT GGT CAC TCT CCT GTT CCC AGC 2310
Leu Ser Gly Glu Gly Lys Gly Pro Gly His Ser Pro Val Pro Ser 770

CAG ACG ACC GAG GTG CCT GTG GGC GCC CTG GGC ATT GCT GTT TCT 2355
Gln Thr Thr Glu Val Pro Val Gly Ala Leu Gly Ile Ala Val Ser 785
```

FIGURE 2A

```
ATG GGG TGG CTT TGC TCT GGG CTC CTG TTC CCT GTG AGC TGC CTG  -31
Met Gly Trp Leu Cys Ser Gly Leu Leu Phe Pro Val Ser Cys Leu  -11

GTC CTG CTG CAG GTG GCA AGC TCT GGG AAC ATG AAG GTC TTG CAG 15
Val Leu Leu Gln Val Ala Ser Ser Gly Asn Met Lys Val Leu Gln  5

GAG CCC ACC TGC GTC TCC GAC TAC ATG AGC ATC TCT ACT TGC GAG 60
Glu Pro Thr Cys Val Ser Asp Tyr Met Ser Ile Ser Thr Cys Glu 20

TGG AAG ATG AAT GGT CCC ACC AAT TGC AGC ACC GAG CTC CGC CTG 105
Trp Lys Met Asn Gly Pro Thr Asn Cys Ser Thr Glu Leu Arg Leu  50

TTG TAC CAG CTG GTT TTT CTG CTC TCC GAA GCC CAC ACG TGT ATC 150
Leu Tyr Gln Leu Val Phe Leu Leu Ser Glu Ala His Thr Cys Ile  50

CCT GAG AAC AAC GGA GGC GCG GGG TGC GTG TGC CAC CTG CTC ATG 195
Pro Glu Asn Asn Gly Gly Ala Gly Cys Val Cys His Leu Leu Met  65

GAT GAC GTG GTC AGT GCG GAT AAC TAT ACA CTG GAC CTG TGG GCT 240
Asp Asp Val Val Ser Ala Asp Asn Tyr Thr Leu Asp Leu Trp Ala  80

GGG CAG CAG CTG CTG TGG AAG GGC TCC TTC AAG CCC AGC GAG CAT 285
Gly Gln Gln Leu Leu Trp Lys Gly Ser Phe Lys Pro Ser Glu His  95

GTG AAA CCC AGG GCC CCA GGA AAC CTG ACA GTT CAC ACC AAT GTC 330
Val Lys Pro Arg Ala Pro Gly Asn Leu Thr Val His Thr Asn Val 110

TCC GAC ACT CTG CTG CTG ACC TGG AGC AAC CCG TAT CCC CCT GAC 375
Ser Asp Thr Leu Leu Leu Thr Trp Ser Asn Pro Tyr Pro Pro Asp 125

AAT TAC CTG TAT AAT CAT CTC ACC TAT GCA GTC AAC ATT TGG AGT 420
Asn Tyr Leu Tyr Asn His Leu Thr Tyr Ala Val Asn Ile Trp Ser 140

GAA AAC GAC CCG GCA GAT TTC AGA ATC TAT AAC GTG ACC TAC CTA 465
Glu Asn Asp Pro Ala Asp Phe Arg Ile Tyr Asn Val Thr Tyr Leu 155

GAA CCC TCC CTC CGC ATC GCA GCC AGC ACC CTG AAG TCT GGG ATT 510
Glu Pro Ser Leu Arg Ile Ala Ala Ser Thr Leu Lys Ser Gly Ile 170

TCC TAC AGG GCA CGG GTG AGG GCC TGG GCT CAG TGC TAT AAC ACC 555
Ser Tyr Arg Ala Arg Val Arg Ala Trp Ala Gln Cys Tyr Asn Thr 185

ACC TGG AGT GAG TGG AGC CCC AGC ACC AAG TGG CAC AAC TCC TAC 600
Thr Trp Ser Glu Trp Ser Pro Ser Thr Lys Trp His Asn Ser Tyr 200

AGG GAG CCC TTC GAG CAG CAC CTC CTG CTG GGC GTC AGC GTT TCC 645
Arg Glu Pro Phe Glu Gln His Leu Leu Leu Gly Val Ser Val Ser 215

AGG GAG CCC TTC GAG CAG CAC CTC CTG CTG GGC GTC AGC GTT TCC 645
Arg Glu Pro Phe Glu Gln His Leu Leu Leu Gly Val Ser Val Ser 215

TGC ATT GTC ATC CTG GCC GTC TGC CTG TTG TGC TAT GTC AGC ATC 690
Cys Ile Val Ile Leu Ala Val Cys Leu Leu Cys Tyr Val Ser Ile 230
```

FIGURE 2B

```
ACC AAG ATT AAG AAA GAA TGG TGG GAT CAG ATT CCC AAC CCA GCC 735
Thr Lys Ile Lys Lys Glu Trp Trp Asp Gln Ile Pro Asn Pro Ala 245

CGC AGC CGC CTC GTG GCT ATA ATA ATC CAG GAT GCT CAG GGG TCA 780
Arg Ser Arg Leu Val Ala Ile Ile Ile Gln Asp Ala Gln Gly Ser 260

CAG TGG GAG AAG CGG TCC CGA GGC CAG GAA CCA GCC AAG TGC CCA 825
Gln Trp Glu Lys Arg Ser Arg Gly Gln Glu Pro Ala Lys Cys Pro 275

CAC TGG AAG AAT TGT CTT ACC AAG CTC TTG CCC TGT TTT CTG GAG 870
His Trp Lys Asn Cys Leu Thr Lys Leu Leu Pro Cys Phe Leu Glu 290

CAC AAC ATG AAA AGG GAT GAA GAT CCT CAC AAG GCT GCC AAA GAG 915
His Asn Met Lys Arg Asp Glu Asp Pro His Lys Ala Ala Lys Glu 305

ATG CCT TTC CAG GGC TCT GGA AAA TCA GCA TGG TGC CCA GTG GAG 960
Met Pro Phe Gln Gly Ser Gly Lys Ser Ala Trp Cys Pro Val Glu 320

ATC AGC AAG ACA GTC CTC TGG CCA GAG AGC ATC AGC GTG GTG CGA 1005
Ile Ser Lys Thr Val Leu Trp Pro Glu Ser Ile Ser Val Val Arg  335

TGT GTG GAG TTG TTT GAG GCC CCG GTG GAG TGT GAG GAG GAG GAG 1050
Cys Val Glu Leu Phe Glu Ala Pro Val Glu Cys Glu Glu Glu Glu  350

GAG GTA GAG GAA GAA AAA GGG AGC TTC TGT GCA TCG CCT GAG AGC 1095
Glu Val Glu Glu Glu Lys Gly Ser Phe Cys Ala Ser Pro Glu Ser  365

AGC AGG GAT GAC TTC CAG GAG GGA AGG GAG GGC ATT GTG GCC CGG 1140
Ser Arg Asp Asp Phe Gln Glu Gly Arg Glu Gly Ile Val Ala Arg  380

CTA ACA GAG AGC CTG TTC CTG GAC CTG CTC GGA GAG GAG AAT GGG 1185
Leu Thr Glu Ser Leu Phe Leu Asp Leu Leu Gly Glu Glu Asn Gly  395

GGC TTT TGC CAG CAG GAC ATG GGG GAG TCA TGC CTT CTT CCA CCT 1230
Gly Phe Cys Gln Gln Asp Met Gly Glu Ser Cys Leu Leu Pro Pro 410

TCG GGA AGT ACG AGT GCT CAC ATG CCC TGG GAT GAG TTC CCA AGT 1275
Ser Gly Ser Thr Ser Ala His Met Pro Trp Asp Glu Phe Pro Ser  425

GCA GGG CCC AAG GAG GCA CCT CCC TGG GGC AAG GAG CAG CCT CTC 1320
Ala Gly Pro Lys Glu Ala Pro Pro Trp Gly Lys Glu Gln Pro Leu  440

CAC CTG GAG CCA AGT CCT CCT GCC AGC CCG ACC CAG AGT CCA CTC 1365
His Leu Glu Pro Ser Pro Pro Ala Ser Pro Thr Gln Ser Pro Leu  455

AAC CTG ACT TGC ACA GAG ACG CCC CTC GTC ATC GCA GGC AAC CCT 1410
Asn Leu Thr Cys Thr Glu Thr Pro Leu Val Ile Ala Gly Asn Pro  470

GCT TAC CGC AGC TTC AGC AAC TCC CTG AGC CAG TCA CCG TGT CCC 1455
Ala Tyr Arg Ser Phe Ser Asn Ser Leu Ser Gln Ser Pro Cys Pro  485

AGA GAG CTG GGT CCA GAC CCA CTG CTG GCC AGA CAC CTG GAG GAA 1500
Arg Glu Leu Gly Pro Asp Pro Leu Leu Ala Arg His Leu Glu Glu  500
```

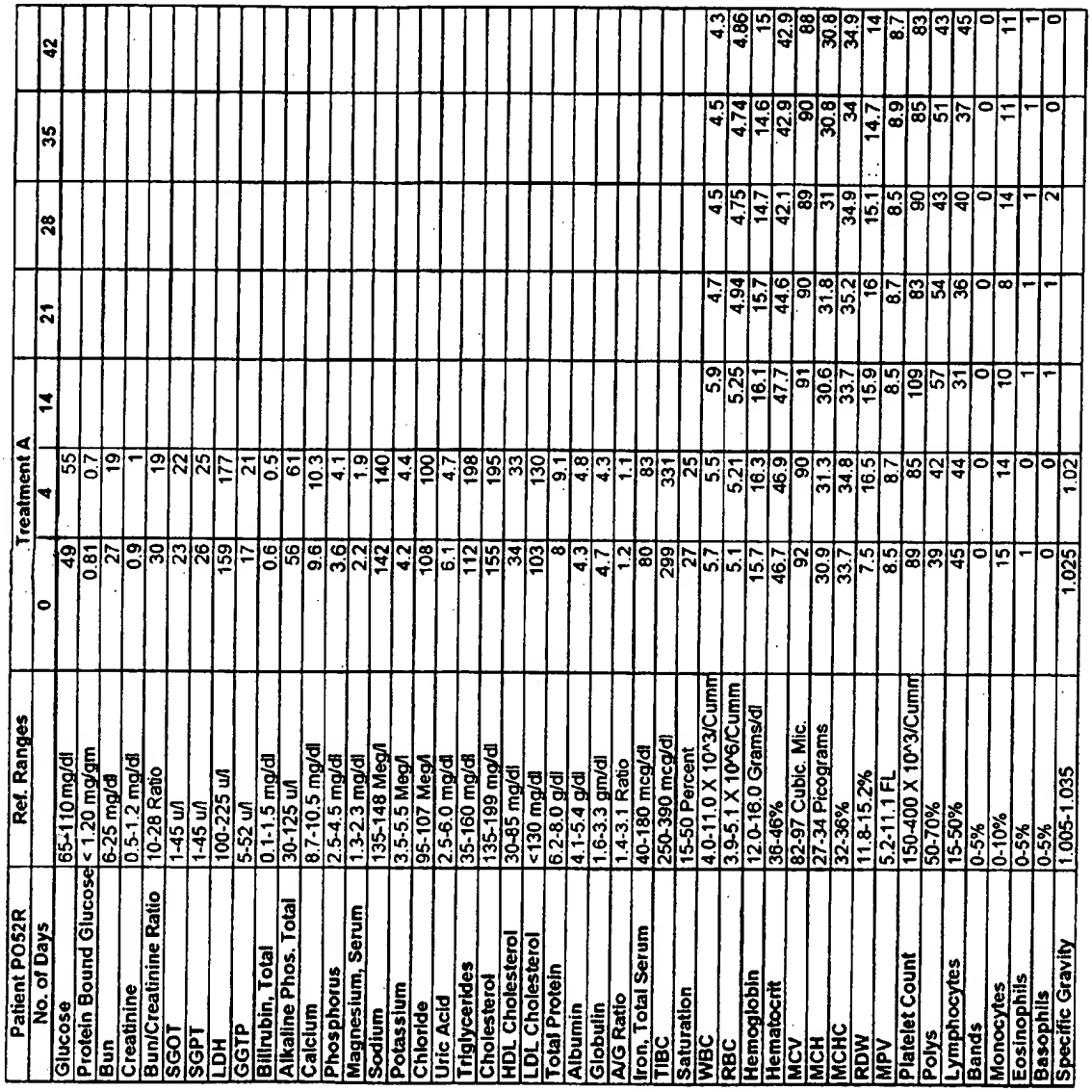
FIGURE 2C

```
GTA GAA CCC GAG ATG CCC TGT GTC CCC CAG CTC TCT GAG CCA ACC 1545
Val Glu Pro Glu Met Pro Cys Val Pro Gln Leu Ser Glu Pro Thr  515

ACT GTG CCC CAA CCT GAG CCA GAA ACC TGG GAG CAG ATC CTC CGC 1590
Thr Val Pro Gln Pro Glu Pro Glu Thr Trp Glu Gln Ile Leu Arg  530

CGA AAT GTC CTC CAG CAT GGG GCA GCT GCA GCC CCC GTC TCG GCC 1635
Arg Asn Val Leu Gln His Gly Ala Ala Ala Ala Pro Val Ser Ala  545

CCC ACC AGT GGC TAT CAG GAG TTT GTA CAT GCG GTG GAG CAG GGT 1680
Pro Thr Ser Gly Tyr Gln Glu Phe Val His Ala Val Glu Gln Gly  560

GGC ACC CAG GCC AGT GCG GTG GTG GGC TTG GGT CCC CCA GGA GAG 1725
Gly Thr Gln Ala Ser Ala Val Val Gly Leu Gly Pro Pro Gly Glu  575

GCT GGT TAC AAG GCC TTC TCA AGC CTG CTT GCC AGC AGT GCT GTG 1770
Ala Gly Tyr Lys Ala Phe Ser Ser Leu Leu Ala Ser Ser Ala Val  590

TCC CCA GAG AAA TGT GGG TTT GGG GCT AGC AGT GGG GAA GAG GGG 1815
Ser Pro Glu Lys Cys Gly Phe Gly Ala Ser Ser Gly Glu Glu Gly  605

TAT AAG CCT TTC CAA GAC CTC ATT CCT GGC TGC CCT GGG GAC CCT 1860
Tyr Lys Pro Phe Gln Asp Leu Ile Pro Gly Cys Pro Gly Asp Pro  620

GCC CCA GTC CCT GTC CCC TTG TTC ACC TTT GGA CTG GAC AGG GAG 1905
Ala Pro Val Pro Val Pro Leu Phe Thr Phe Gly Leu Asp Arg Glu  635

CCA CCT CGC AGT CCG CAG AGC TCA CAT CTC CCA AGC AGC TCC CCA 1950
Pro Pro Arg Ser Pro Gln Ser Ser His Leu Pro Ser Ser Ser Pro  650

GAG CAC CTG GGT CTG GAG CCG GGG GAA AAG GTA GAG GAC ATG CCA 1995
Glu His Leu Gly Leu Glu Pro Gly Glu Lys Val Glu Asp Met Pro  665

AAG CCC CCA CTT CCC CAG GAG CAG GCC ACA GAC CCC CTT GTG GAC 2040
Lys Pro Pro Leu Pro Gln Glu Gln Ala Thr Asp Pro Leu Val Asp  680

AGC CTG GGC AGT GGC ATT GTC TAC TCA GCC CTT ACC TGC CAC CTG 2085
Ser Leu Gly Ser Gly Ile Val Tyr Ser Ala Leu Thr Cys His Leu  695

TGC GGC CAC CTG AAA CAG TGT CAT GGC CAG GAG GAT GGT GGC CAG 2130
Cys Gly His Leu Lys Gln Cys His Gly Gln Glu Asp Gly Gly Gln  710

ACC CCT GTC ATG GCC AGT CCT TGC TGT GGC TGC TGC TGT GGA GAC 2175
Thr Pro Val Met Ala Ser Pro Cys Cys Gly Cys Cys Cys Gly Asp  725

AGG TCC TCG CCC CCT ACA ACC CCC CTG AGG GCC CCA GAC CCC TCT 2220
Arg Ser Ser Pro Pro Thr Thr Pro Leu Arg Ala Pro Asp Pro Ser  740

CCA GGT GGG GTT CCA CTG GAG GCC AGT CTG TGT CCG GCC TCC CTG 2265
Pro Gly Gly Val Pro Leu Glu Ala Ser Leu Cys Pro Ala Ser Leu  755

GCA CCC TCG GGC ATC TCA GAG AAG AGT AAA TCC TCA TCA TCC TTC 2355
Ala Pro Ser Gly Ile Ser Glu Lys Ser Lys Ser Ser Ser Ser Phe  770
```

FIGURE 2D

```
CAT CCT GCC CCT GGC AAT GCT CAG AGC TCA AGC CAG ACC CCC AAA 2310
His Pro Ala Pro Gly Asn Ala Gln Ser Ser Ser Gln Thr Pro Lys  785

ATC GTG AAC TTT GTC TCC GTG GGA CCC ACA TAC ATG AGG GTC TCT 2400
Ile Val Asn Phe Val Ser Val Gly Pro Thr Tyr Met Arg Val Ser  800
```

Figure 3 (A)



Patient PO52R	Ref. Ranges	Treatment A						
No. of Days		0	4	14	21	28	35	42
Glucose	65-110 mg/dl	49	55					
Protein Bound Glucose	< 1.20 mg/gm	0.81	0.7					
Bun	6-25 mg/dl	27	19					
Creatinine	0.5-1.2 mg/dl	0.9	1					
Bun/Creatinine Ratio	10-28 Ratio	30	19					
SGOT	1-45 u/l	23	22					
SGPT	1-45 u/l	26	25					
LDH	100-225 u/l	159	177					
GGTP	5-52 u/l	17	21					
Bilirubin, Total	0.1-1.5 mg/dl	0.6	0.5					
Alkaline Phos. Total	30-125 u/l	56	61					
Calcium	8.7-10.5 mg/dl	9.6	10.3					
Phosphorus	2.5-4.5 mg/dl	3.6	4.1					
Magnesium, Serum	1.3-2.3 mg/dl	2.2	1.9					
Sodium	135-148 Meq/l	142	140					
Potassium	3.5-5.5 Meq/l	4.2	4.4					
Chloride	95-107 Meq/l	108	100					
Uric Acid	2.5-6.0 mg/dl	6.1	4.7					
Triglycerides	35-160 mg/dl	112	198					
Cholesterol	135-199 mg/dl	155	195					
HDL Cholesterol	30-85 mg/dl	34	33					
LDL Cholesterol	<130 mg/dl	103	130					
Total Protein	6.2-8.0 g/dl	8	9.1					
Albumin	4.1-5.4 g/dl	4.3	4.8					
Globulin	1.6-3.3 gm/dl	4.7	4.3					
A/G Ratio	1.4-3.1 Ratio	1.2	1.1					
Iron, Total Serum	40-180 mcg/dl	80	83					
TIBC	250-390 mcg/dl	299	331					
Saturation	15-50 Percent	27	25					
WBC	4.0-11.0 X 10^3/Cumm	5.7	5.5	5.9	4.7	4.5	4.5	4.3
RBC	3.9-5.1 X 10^6/Cumm	5.1	5.21	5.25	4.94	4.75	4.74	4.86
Hemoglobin	12.0-16.0 Grams/dl	15.7	16.3	16.1	15.7	14.7	14.6	15
Hematocrit	36-46%	46.7	46.9	47.7	44.6	42.1	42.9	42.9
MCV	82-97 Cubic. Mic.	92	90	91	90	89	90	88
MCH	27-34 Picograms	30.9	31.3	30.6	31.8	31	30.8	30.8
MCHC	32-36%	33.7	34.8	33.7	35.2	34.9	34	34.9
RDW	11.8-15.2%	7.5	16.5	15.9	16	15.1	14.7	14
MPV	5.2-11.1 FL	8.5	8.7	8.5	8.7	8.5	8.9	8.7
Platelet Count	150-400 X 10^3/Cumm	89	85	109	83	90	85	83
Polys	50-70%	39	42	57	54	43	51	43
Lymphocytes	15-50%	45	44	31	36	40	37	45
Bands	0-5%	0	0	0	0	0	0	0
Monocytes	0-10%	15	14	10	8	14	11	11
Eosinophils	0-5%	1	0	1	1	1	1	1
Basophils	0-5%	0	0	1	1	2	0	0
Specific Gravity	1.005-1.035	1.025	1.02					

Figure 3 (B)

Patient PO52R	Ref. Ranges	Treatment A						
No. of Days		0	4	14	21	28	35	42
Color		Yellow	Straw					
Appearance		Clear	Clear					
PH	4.5-7.5	5	5					
Glucose, Urine	Negative	Neg	Neg					
Protein, Urine	Negative	Neg	Neg					
Acetone, Urine	Negative	Neg	Neg					
Occult Blood	Negative	Neg	Neg					
Bilirubin	Negative	Neg	Neg					
Urobilinogen	0.2-1.0 mg/dl	0.2	0.2					
Leukocyte Esterase	Negative	Neg	Neg					
Nitrite	Negative	Neg	Neg					
WBC Urine	0-5/HPF	0	0					
RBC, Urine	0-3/HPF	0	0					
Epithelial	/HPF							
Bacteria	0/HPF	0	0					
Casts	None/LPF	None	None					
Urine, Microscopic								
Direct Lymphocyte Count	1100-3000 Cells/Cumm	2007	2175	1814	1460	1577	1700	1504
Total T (CD3)	51-87 Percent	86	91	93	87	88	84	89
Total T (Absolute #)	510-3240 #/ul	1716	1983	1681	1266	1392	1428	1334
Helper T (CD4)	31-59 Percent	10	11	12	11	11	9	10
Helper T (Absolute #)	537-1571 #/ul	202	237	212	165	172	156	142
Suppressor T (CD8)	13-33 Percent	69	79	82	73	76	67	74
Suppressor T (Abs #)	235-753 #/ul	1387	1713	1485	1064	1197	1138	1113
Helper/Suppressor	1.2-3.8	0.1	0.1	0.1	0.2	0.1	0.1	0.1
Chol/HDL Risk Ratio	Ratio	4.5	5.9					
HIV-1 RNA by PCR Qt.	<400 Copies/ml	15384	52972	157812	122532	159402	121591	573538
HIV RNA by PCR Log 10	<2.6 Copies/ml	4.2	4.7	5.2	5.1	5.2	5.1	5.8
IgG Serum	800-1800 mg/dl	2550	2230					
IgA Serum	90-450 mg/dl	362	333					
IgM Serum	60-280 mg/dl	528	458					
Interferon Gamma		0.1	0					
Interleukin-2	<30 pg/ml	<30	<30					
Interleukin-12		<10	<10					
Interleukin-4								
IL-10		7.3	5.1					
Toxo IgG Serum						1		
Toxo IgM Serum						0.28		
Hep B Surf Antigen						Negative		
Hep C Antibody						Negative		
Hep B Surf Antibody						Positive		
Hep A Total (IGG + IGM)						Positive		
Hep B Core AB, Total						Negative		
Hepatitis A, IGM						Negative		
HBSAB Units, Qual.						>15		
Neutrophils	50-70 FL							
HIV 1 RNA by bDNA-Nichols	<500 Copies/mL							

Figure 3(C)

Patient PO52R					TREATMENT B		TREATMENT C
No. of Days	49	57	92	190	194	202	208
Glucose					100	94	122
Protein Bound Glucose							
Bun					18	21	27
Creatinine					1	1.2	1.1
Bun/Creatinine Ratio					18	17.5	24.5
SGOT					28	26	19
SGPT					21	23	20
LDH					196	142	137
GGTP					18	17	18
Billrubin, Total					0.7	0.6	0.9
Alkaline Phos. Total					55	50	48
Calcium					10.2	9.4	9.8
Phosphorus					5	3.5	3.7
Magnesium, Serum					2.1	1.9	2
Sodium					140	142	142
Potassium					4.1	4.1	3.8
Chloride					111	109	101
Uric Acid					5.9	7.1	7.6
Triglycerides					509	233	198
Cholesterol					272	225	230
HDL Cholesterol					35	37	46
LDL Cholesterol						141	144
Total Protein					9.3	7.5	7.4
Albumin					4.7	4.2	4.3
Globulin					4.6	3.3	3.1
A/G Ratio					1	1.3	1.4
Iron, Total Serum					68	94	92
TIBC							
Saturation							
WBC	4.1	5.2	5.9	5.4	5.2	6.5	6.3
RBC	5.01	5.27	5.07	3.75	3.95	4	4.41
Hemoglobin	15.7	15.7	15.9	14.1	15.5	15.4	16.1
Hematocrit	45.4	47.2	46.9	42.9	44.2	44.9	48.8
MCV	90	90	92	114	112	112	111
MCH	31.2	29.8	31.3	37.5	39.3	38.5	36.5
MCHC	34.5	33.2	33.9	32.8	35.1	34.2	33
RDW	14.8	14	19	13.7	13.1	12.6	13.2
MPV	8.9	9.4	9.3	8.2	8.5	7.8	8.6
Platelet Count	81	88	58	179	128	132	139
Polys	52	56	57				
Lymphocytes	32	32	30	43	31	31	30
Bands	0	0	0				
Monocytes	13	9	10	12	13	10	8
Eosinophils	2	1	2	1	1	1	1
Basophils	1	2	1	0	0	1	0
Specific Gravity							

FIGURE 3(D)

Patient PO52R					TREATMENT B		TREATMENT C
No. of Days	49	57	92	190	194	202	208
Color							
Appearance							
PH							
Glucose, Urine							
Protein, Urine							
Acetone, Urine							
Occult Blood							
Billrubin							
Urobilinogen							
Leukocyte Esterase							
Nitrite							
WBC Urine							
RBC, Urine							
Epithelial							
Bacteria							
Casts							
Urine, Microscopic							
Direct Lymphocyte Count	1248	1704	1732	1828	1593	1888	
Total T (CD3)	94	89	87	86	88	85	
Total T (Absolute #)	1174	1508	1504	1567	1402	1609	
Helper T (CD4)	12	13	12	13	11	15	
Helper T (Absolute #)	152	216	203	245	177	276	
Suppressor T (CD8)	83	70	69	70	73	67	
Suppressor T (Abs #)	1035	1195	1200	1276	1167	1255	
Helper/Suppressor	0.1	0.2	0.2	0.2	0.2	0.2	
Chol/HDL Risk Ratio					7.8	6.1	5
HIV-1 RNA by PCR Qt.	193073	10096	1481262	2960	77626	7467	<400
HIV RNA by PCR Log 10	5.3		6.2	3.5	4.9	3.9	<2.6
IgG Serum					1920	1650	1590
IgA Serum					689	437	408
IgM Serum					512	357	417
Interferon Gamma					0		
Interleukin-2							
Interleukin-12							
Interleukin-4					0		
IL-10							
Toxo IgG Serum							
Toxo IgM Serum							
Hep B Surf Antigen							
Hep C Antibody							
Hep B Surf Antibody							
Hep A Total (IGG + IGM)							
Hep B Core AB, Total							
Hepatitis A, IGM							
HBSAB Units, Qual.							
Neutrophils				44	55	59	61
HIV 1 RNA by bDNA-Nichols				3203			2107